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ORIGINAL ARTICLE

Association of testosterone levels and heroin usage characteristics in male heroin users

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Abstract

BACKGROUND: Previous studies have shown that heroin abuse can alter the gonadal functions. Few studies examined the association between testosterone levels and heroin use in the existing literature. We aimed to determine the association between gonadal hormones and heroin usage characteristics over 12 weeks of abstinence in heroin users.
METHODS: We collected data on patient demographics and heroin use patterns for 65 men aged 18 to 45 and for 29 age-matched healthy controls. Serum levels of total testosterone, estradiol, and prolactin were assessed at 5 time points.
RESULTS: Testosterone levels gradually increased and prolactin levels decreased in heroin users in this study. In heroin users, a significant positive correlation was observed between the way of using drug and the testosterone levels, the way of using drug and the estradiol levels, between the duration of heroin dependence and the testosterone levels, between the duration of heroin dependence and the estradiol levels on D0, and between relapse time and testosterone levels on D84.
CONCLUSIONS: Our data reveal testosterone might promote injection drug use and repeated relapse in male heroin users.

INTRODUCTION

Heroin abuse is a major public health problem and a chronic medical illness. Many studies have reported altered function of the hypothalamic-pituitary-gonadal (HPG) axis in heroin users (Brown *et al.* 2006; Wisniewski *et al.* 2007). Furthermore, gonadal hormone levels, particularly testosterone, are also altered (Wisniewski *et al.* 2007). Hypogonadism is a common comorbidity, and may result in cognitive abnormalities, affecting the quality of life and possibly decreasing adherence to treatment (Wisniewski *et al.* 2007; Dackis & Gold 1985; Zilbermint *et al.* 2013).

Testosterone and estradiol are sex steroids that affect skeletal muscles, body composition, and sexual function (Mooradian *et al.* 1987). Furthermore, they regulate social behaviors (Booth *et al.* 2006; Takahashi 2012; King *et al.* 2005). Sex steroid receptors are found throughout the prefrontal cortex and limbic brain areas, which mediate addictive behavior-linked reward responsiveness, risk-taking, and cognitive control (Simerly *et al.* 1990). A study reported that sex steroids might

promote alcohol use by stimulating brain areas implicated in reward processing (Erik *et al.* 2013).

We hypothesized that sex steroids may regulate heroin usage characteristics in heroin users. Therefore, we evaluated changes in gonadal hormones in abstinent patients over a consecutive 12-week period by measuring testosterone and estradiol concentrations. Prolactin was also evaluated, because its release induces a negative feedback loop regulating testosterone secretion. To determine this relationship between heroin usage characteristics and gonadal dysfunction, we collected information on patient demographics and heroin use patterns.

MATERIAL AND METHODS

Patients and ethics

This study was carried out at the Compulsory Detoxification Center of Sichuan Province in China. Sixty-five male patients with heroin addiction were recruited between March 2009 and June 2010 in a controlled setting, meeting the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, standards. Participants remained free from opioids for at least 12 weeks without pharmacological heroin detoxification.

The inclusion criteria were as follows: 1) patients with heroin dependence that met the criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); 2) aged 18 to 45 years; 3) a heroin-positive urine analysis detected by thin-layer chromatography, final drug intake within the last 8 to 36 hours before entry to the study; and 4) written informed consent. Exclusion criteria were as follows: serious opiate withdrawal symptoms, including disturbance of consciousness, serious violence, and severe dehydration; attempted suicide, current psychiatric illnesses and dementia; serious infectious diseases, serious disease of the heart, lung, kidney, liver, central nervous system and hematopoietic cancer; and unable to understand the consent process. Twenty-nine age-matched male healthy controls who had never used illicit psychotropic drugs or misused alcohol, were recruited from the local community. All participants were screened with the Structured Clinical Interview for DSM-IV disorder (SCID), physical examination, urine drug screens, and electrocardiogram.

This study was approved by the Medical Ethics Committee of West China Hospital of Sichuan University, and the trial conformed to the principles of the Declaration of Helsinki. All patients signed informed consent forms and were able to withdraw from the study at any time.

Determination

Blood samples from 65 patients were collected at baseline (day 0, D0) and on D10, D28, D56, and D84 at about the same time (9 AM). Blood samples were maintained in non-heparinized tubes immediately after being drawn, allowed to clot at 37 °C for 5 min, and centrifuged at 2 500 rpm for 15 min. The serum was separated and stored at −70 °C until tests were conducted at West China Hospital. Testosterone, estradiol, and prolactin were measured by liquid chromatography tandem mass spectrometry (LC-MS). Only one blood draw was made for each control subject. Heroin usage characteristics were recorded by the trained psychiatrist, utilizing the structural interviews and questionnaires.

Tests were done by a technician who was blinded to the identity of the samples.

Statistical analysis

All data were documented with Epidata 3.0 by two independent individuals and were secured after checking. Data were analyzed with SPSS version 19.0. The data for patients' characteristics (including age, duration of heroin dependence, the length of abstinence from last drug use, amount of last drug use, and the average daily amount of use for the past week at baseline) are presented as the mean±standard deviation. The Student's *t*-test was used for age. The repeated-measures analysis of variance test was performed to evaluate significant differences in gonadal hormones. Linear correlation statistics between gonadal hormones and heroin usage characteristics were calculated on D0 and D84. Statistical significance was preset at 0.05 using a two-tailed test.

RESULTS

Patient characteristics are shown in Table 1, including duration of heroin dependence, method of drug use, time from last use, amount of last use, relapse time, and the average daily amount used during the past week. The statistical analysis between the two groups showed that they were comparable in age (28.82±4.05 years vs. 28.10±5.29 years, p=0.477).

Testosterone levels were significantly lower in heroin users (4.94±1.68 ng/ml) than in healthy controls (6.08±1.79 ng/ml) on D0 (p=0.004, Figure 1A). However, compared to healthy controls, heroin users displayed significantly higher testosterone levels during the 12 week follow-up (7.26±2.69 ng/ml, p=0.033 on D84).

Like testosterone, estradiol levels in heroin users (31.45±9.52 ng/ml) were significantly lower than in healthy controls (37.13±10.35 ng/ml,) at D0 (p=0.011). However, compared to healthy controls, heroin users displayed significantly higher estradiol levels during the 12-week follow-up (46.97±11.05 ng/ml, p<0.001 on D84).

The mean prolactin level in heroin users was less than 10 ng/ml, which was significantly lower than that of healthy controls (14.17±6.08 ng/ml) over the 12 week study (p<0.001, Figure 1C).

In heroin users, a significant, positive correlation was observed between the way of using drug and the testosterone levels (correlation coefficient: 0.278, p=0.002),

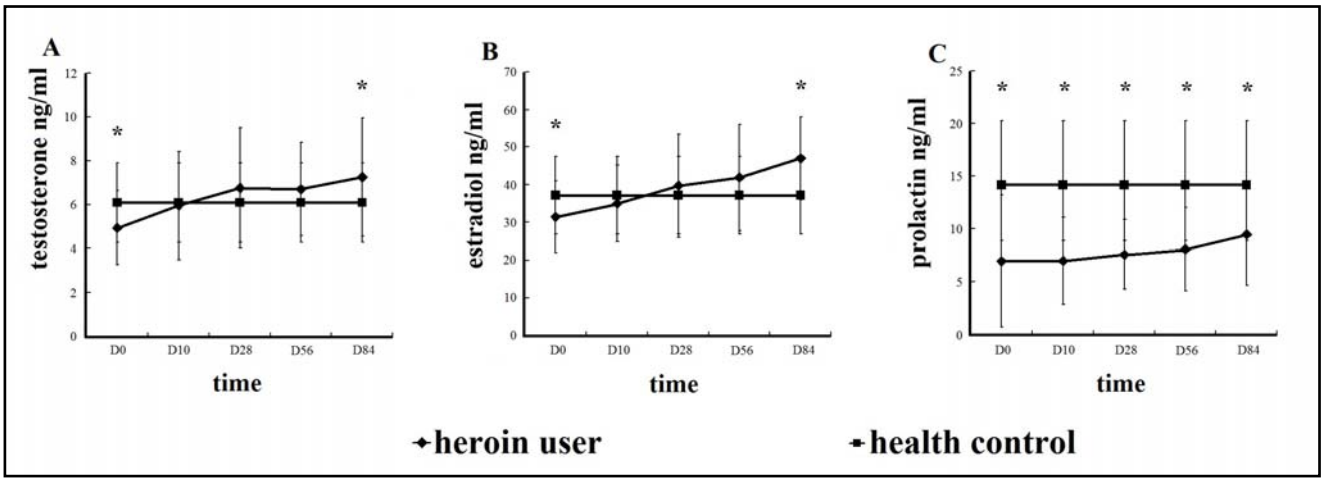

Fig. 1. Changes in gonadol hormone in heroin users and healthy controls. Changes in testosterone (A), estradiol (B), and prolactin (C) during 12 weeks. Data are presented as the mean±SEM for each time point. *p<0.05, healthy control (n=28) and heroin users (n=65).

between the way of using drug and the estradiol levels (correlation coefficient: 0.451, p<0.001), between the duration of heroin dependence and the testosterone levels (correlation coefficient: 0.254, p=0.004), between the duration of heroin dependence and the estradiol levels (correlation coefficient: 0.220, p=0.013) on D0, between the relapse time and the testosterone levels (correlation coefficient: 0.300, p=0.014), and between the way of using drug and the estradiol levels (correlation coefficient: 0.383, p=0.002) on D84. A marginal correlation was observed between the relapse time and the estradiol levels (correlation coefficient: 0.235, p=0.058; Table 2, Table 3) on D84.

Tab. 1. Characteristics of patients with heroin dependence.

Demographic data	Heroin users
Duration of heroin dependence (months)	82.95±61.68
Daily heroin intake (g) during the past week	0.48±0.54
Way of using drug (with cigarettes/ injection/ other way)	21/44/0
Time from the last use (hours)	19.21±6.26
Amounts of the last use (g)	0.25±0.12

Data are shown as the number or the mean±SD.

Tab. 2. The correlation between the different parameters in the heroin users on D0.

	Time of relapse		Way of using drug		Duration of heroin dependence (month)		Daily heroin intake (g)	
	p-value	Pearson Correlation	*p*-value	Pearson Correlation	*p*-value	Pearson Correlation	*p*-value	Pearson Correlation
testosterone	0.503	0.060	0.002	0.278	0.004	0.254	0.594	–0.048
estradiol	0.356	0.083	<0.001	0.451	0.013	0.220	0.326	0.088
prolactin	0.380	–0.079	0.871	0.015	0.730	0.031	0.506	–0.060

Tab. 3. The correlation between the different parameters in the heroin users on D84.

	Time of relapse		Way of using drug		Duration of heroin dependence (month)		Daily heroin intake (g)	
	p-value	Pearson Correlation	*p*-value	Pearson Correlation	*p*-value	Pearson Correlation	*p*-value	Pearson Correlation
testosterone	0.014	0.300	0.515	0.083	0.224	0.143	0.093	0.205
estradiol	0.058	0.235	0.002	0.383	0.273	0.135	0.595	0.066
prolactin	0.200	–0.160	0.680	–0.053	0.677	–0.051	0.944	0.009

DISCUSSION

The aim of the present study was to determine whether gonadal hormones levels are associated with heroin usage characteristics in abstinent heroin users. During the acute withdrawal period, we found that testosterone, estradiol, and prolactin levels are significantly lower in heroin users, and that higher testosterone and estradiol levels are associated with longer duration of heroin dependence and injection drug use. The testosterone and estradiol gradually increased during the 12-week follow-up. At the end of the present study, we found that higher sex steroids levels are associated with an increased number of relapses.

Consistent with the present study, decreased plasma testosterone in heroin users has been well documented in previous studies (Brown *et al.* 2006; Wisniewski *et al.* 2007; Dackis & Gold 1985; Zilbermint *et al.* 2013). However, unlike our study, these studies reported that hyperprolactinemia occurs in chronic cocaine users (Dackis and Gold, 1985) and in heroin users (Zhang *et al.* 2014). Wisniewski reported that estradiol concentrations did not differ according to drug use status (active users and nonusers) (Wisniewski *et al.* 2007). These discrepant findings might be attributed to sex differences between participants across studies, since only male participants were recruited in the present study.

Few studies have demonstrated the association between sex steroids levels and heroin usage characteristics during withdrawal period. We showed that higher testosterone levels are associated with an increased number of relapses, injection drug use, and longer term duration of heroin dependence in abstinent heroin users. Testosterone might be a risk factor for drug use. Higher testosterone levels are associated with increased activation of the reward-associated brain area in adolescents (Op de Macks *et al.* 2011), stimulating sensation-seeking behavior (Steinberg, 2008). Moreover, testosterone levels are positively correlated with aggression in man and woman (Leo *et al.* 2014; Takahashi *et al.* 2006; Pivovarciova *et al.* 2014). Aggressive behavior was reported as an antecedent for future drug use in males, and may help determine the likelihood of persistent drug use in adulthood (Ensminger *et al.* 2002). The enzyme aromatase catalyzes testosterone into estradiol, and this emzyme regulates addictive behaviors (Lenz *et al.* 2011), which may explain the marginal correlation between estradiol levels and relapse time.

Prolactin, which increased in humans undergoing psychological stress (Sonino *et al.* 2004; Uhart *et al.* 2006), attenuates stress-induced neuroendocrine and anxiety responses (Torner *et al.* 2002). This increase in prolactin may be an adaptation that ensures immune system functionality (Lee, 2002) and proper physiological and behavioral responses to stress (Torner *et al.* 2002). Hypoprolactinemia was noted in heroin users in our 12-week study, which may be considered a loss of stress response.

Due to the cross-sectional design of the present study, the causation between testosterone levels and relapse remains unspecified. It is possible that several relapses lead to alterations in gonadal function. Alternatively, increases in testosterone levels may lead to benefits during stressful situations, such as enhanced learning, persistence, focusing on goals, reinforcing successful competition behavior, increased self-efficacy, and better performance (Boksem *et al.* 2013; Schultheiss *et al.* 2002; Turan *et al.* 2014; Flegr & Príplatová 2010), which perhaps promotes heroin withdrawal. Those abstinent heroin users that do not adhere to withdrawal may relapse again. Nevertheless, Mihail reported that sex steroids were not related to cognitive performance in men with substance use (Mihail *et al.* 2013).

Several limitations need to be addressed. Firstly, abstinent participants in a controlled setting may be different from those in a free-living environment, which could limit the generalizability of the findings. Moreover, additional biological indices should be considered in a larger, homogeneous sample of heroin-dependent patients in future studies. Finally, self-report for illicit drug use information is another limitation of the present study.

CONCLUSION

Our study reveals an association between heroin usage characteristics and the testosterone levels over 12 weeks of abstinence after acute withdrawal in heroin users. Sex steroids may regulate heroin usage characteristics in heroin users. Testosterone might promote injection drug use and repeated relapse in male heroin users.

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