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Serum glial cell line-derived neurotrophic factor levels and impulsivity in heroin addiction: a cross-sectional, case-control study of 129 heroin addicts

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ABSTRACT

OBJECTIVE: Glial cell line-derived neurotrophic factor (GDNF), being a protective of dopaminergic neurons, is reported to modulate addictive behaviours and have a role as a negative regulator for biochemical and behavioural adaptations to drug abuse. We aimed to reveal impulsivity and serum GDNF levels in patients with heroin addiction and investigate their relationships in order to contribute to the understanding of behavioural aspects and biological mechanisms in heroin addiction via this study.

METHODS: This study was performed at the Department of Psychiatry of Ankara Numune Training and Research Hospital, Turkey. We recruited 129 heroin-dependent patients and 90 age, sex, and smoking-matched healthy controls with no major psychopathology. Barratt Impulsivity Scale-11, Hospital Anxiety and Depression Scale (HADS) and sociodemographic data form were applied to all participants. Laboratory analysis for serum GDNF levels was performed for each participant's blood sample.

RESULTS: Total impulsivity scores and scores of Attentional Impulsivity, Motor Impulsivity, and Unplanned Impulsivity subscales were all higher in heroin addicts compared to the controls. Heroin addicts had also lower serum GDNF levels and lower GDNF levels were associated with high impulsivity and high HADS scores in heroin addicts.

CONCLUSION: Decrement in GDNF levels in heroin addiction seems as to be an important data which could be associated with impulsivity, anxiety, and depressive symptoms. GDNF could find a prominent place among the target molecules in the treatment of heroin addiction.

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Heroin addiction; glial cell line-derived neurotrophic factor; GDNF; impulsivity; anxiety; depression

Introduction

Neurotrophic factors have an important role in the growth and differentiation of neurons during development and have been implicated in many forms of plasticity within the adult central nervous system.

The glial cell line-derived neurotrophic factor (GDNF) is one of the most potent neurotrophic factors influencing the dopaminergic system. It is reported that GDNF has distinct protective effects on the survival of midbrain dopaminergic neurons in both *in vitro* and *in vivo* studies [1–4]. Preclinic studies demonstrated that GDNF was protective of dopaminergic neurons when administered in advance of degenerative toxins, and it also may have restorative effects on dying dopaminergic neurons [5].

Neurotrophic factors and especially GDNF have raised considerable hope to be able to stop the progressive degeneration in neuropsychiatric diseases such as Parkinson Disease and Alzheimer Disease [6]. Besides, animal studies indicate that GDNF modulates addictive behaviours and the role of GDNF as a

negative regulator for biochemical and behavioural adaptations to drug abuse was reported [7]. Opiate withdrawal was shown to regulate the expression levels of several neurotrophic factors in specific regions of adult brain [8]. The rewarding effects and/or self-administration of cocaine and ethanol were found to be associated with up-regulation of GDNF levels in the ventral tegmental area (VTA) or striatum [9,10].

Messer et al. reported a functional interaction between GDNF and drugs of abuse at the level of the mesolimbic dopamine system and emphasized complex mechanisms that were likely to be induced in brain by chronic exposure to a drug of abuse [11].

Garnicella et al. found that GDNF was highly effective in reducing heavy alcohol drinking and GDNF in VTA was more effective in inhibiting reacquisition of ethanol self-administration after the extinction period than in reducing ethanol self-administration before the period of abstinence [12]. So, these findings were stated to suggest an important protective role for GDNF in abstinence and relapse processes.

In light of these data, we aimed to search on GDNF levels and heroin addiction which is a growing serious health problem in the world. We focused on GDNF because GDNF has so far more potent effects on the survival and protection of dopaminergic neurons compared to brain-derived neurotrophic factor (BDNF) and other neurotrophins [3] and GDNF enhances the survival of midbrain dopamine neurons *in vivo* after being exposed to dopaminergic neurotoxins such as 6-hydroxydopamine in an obvious way [1]. Additionally, it was shown that a single injection of GDNF into the midbrain could exert protective effects for at least a month [2,13].

Traits that are related to the extensive construct of disinhibition such as sensation seeking, impulsivity, and behavioural under control have been found to predict substance misuse disorders in adults and it is reported to be higher in substance-dependent patients [14,15].

Pompili et al. reported that substance-dependent patients have higher hopelessness, global psychopathology severity, impulsivity/aggression, and they are frequently depressed [16].

As far as we know, there are no studies in the literature related to the association between GDNF levels, impulsivity, and clinical characteristics in heroin-dependent patients. Evidence-based data related to impulsive personality traits to the development and maintenance of substance misuse problems have been rising [17–19].

We aimed to reveal impulsivity and serum GDNF levels in patients with heroin addiction and investigate their relationships in order to contribute the understanding of behavioural aspects and biological mechanisms in heroin addiction via this study.

Methods

Participants

This study was performed at the Department of Psychiatry of Ankara Numune Training and Research Hospital, Turkey. We recruited 129 heroin-dependent patients who admitted to our addiction clinic between January 2015 and May 2015; and 90 age, sex, and smoking-matched healthy controls with no major psychopathology.

Inclusion criteria for the heroin-dependent group were a diagnosis of heroin dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, 18–65 years of age, and possessing at least five years of primary school education.

The exclusion criteria included anoxia or hypoxia during birth; the presence of a major medical disorder or neuropsychiatric symptoms secondary to a metabolic disorder or structural lesion and any comorbid psychiatric disorders in the heroin-dependent group.

We did a cross-sectional study to investigate the impulsivity and serum GDNF levels in heroin-dependent patients. The study received approval by the local ethics committee.

Every participant was examined by two trained psychiatrists after obtaining informed consent. Sociodemographic data form and the Barratt Impulsiveness Scale were applied to all participants.

Barratt Impulsivity Scale-11

The Barratt Impulsivity Scale (BIS) was developed by Barratt in 1959 and over time it has undergone many revisions. The latest form-11 was developed in 1995 [20]. The scale consists of 30 items and 3 subscales: Attentional Impulsivity (AI), Motor impulsivity (MI), and Unplanned Impulsivity (UI). BIS evaluated four different sub-scores obtained; total points, UI, AI, and MI. High BIS scores are increased levels of the impulsivity index. Validity and reliability study in Turkey was performed by Güleç et al. in 2008 and they reported internal consistency rates (Cronbach's alpha) as 0.82 for total score, 0.80, 0.70, and 0.64 for UI, MI, and AI subscales, respectively [21]. In this study, the scoring key suggested by Patton et al. was used to evaluate the scale [20].

Sociodemographic data form

Sociodemographic data were used in order to describe characteristics of patients and to determine differences among the groups. The form included age, sex, birth place, living place, education years, marital status, family type, occupation, monthly income, history of military service, history of prison, self and family history of physical and psychiatric diseases, first administration date, history of nicotine, alcohol, cannabis, cocaine and other illicit drugs used, detailed history of heroin usage (dosage, duration, dosage, etc.), and history of addiction treatment trials.

Blood samples and laboratory analysis

With informed consent of patients, 10 cm³ of peripheral venous blood samples was taken, placed in gel-containing tubes and centrifuged at 4000 rpm for 10 min to analyse the separated serum. Haemolysed and icteric serums were not used in this study.

Serum GDNF levels were evaluated with a commercial ELISA kit (BOSTER, Boster Biological Technology Co. Ltd, Fremont, CA, Code: EK0362, LOT: 851034314901). Its %CV value was <10, the measurement interval was 31.2–2000 pg/mL and sensitivity was <4 pg/mL.

Statistical analyse

All statistical analyses were performed with IBM SPSS ver.22.0. The Shapiro Wilk test was used as the

normality test. Continuous variables were the Mann–Whitney *U* test when the data were not normally distributed. Categorical variables were compared using Pearson's chi-squared test, the Fisher–Freeman–Halton test, and Fisher's exact test. Correlations between variables were tested using Spearman correlation coefficients. A *p*-value <.05 was considered as significant.

Results

Overall, 129 heroin addicts and 90 healthy controls were enrolled. Demographic and clinical characteristics of two groups are contrasted in Table 1. There were no significant differences among the groups in age, gender, educational level, occupation, marital status, family construct, monthly income, and alcohol and nicotine consumption. Family history of addiction and history of prison rate were higher in the patient group ($p = .024$ and $p = .000$ respectively).

Impulsivity

Total impulsivity scores and scores of AI, MI, and UI subscales were all significantly higher in heroin addicts as shown in Table 2.

GDNF

GDNF levels showed a significant statistical difference between heroin addicts and control groups ($p = .002$). Heroin addicts had lower levels of GDNF

Table 1. Demographic characteristics of heroin addicts and controls.

Variables	Heroin addicts (<i>n</i> = 129)	Controls (<i>n</i> = 90)	<i>p</i>
Age, mean ± SD (min–max)	25.1 ± (17–46)	24.9 ± (17–47)	>.05
Gender			>.05
Male	119 (92.2%)	83 (92.2%)	
Female	10 (7.8%)	7 (7.8%)	
Education			>.05
Primary School	92 (71.9%)	47 (65.3%)	
High School	28 (21.9%)	19 (26.4%)	
College/University	8 (6.3%)	6 (8.3%)	
Marital Status			>.05
Married	25 (74.4%)	45 (65.2%)	
Single	96 (19.4%)	18 (26.1%)	
Divorced	8 (6.2%)	6 (8.7%)	
Smoking (pack year)	9.9 ± 7.5	9.8 ± 6.8	>.05

Table 2. BIS scores in heroin addicts and controls.

Variables	Heroin addicts (mean ± SD)	Controls (mean ± SD)	<i>p</i>
AI	15.4 ± 4.6	11.1 ± 3.3	<.001
MI	22.6 ± 8.7	15.2 ± 4.9	<.001
UI	25.6 ± 9.4	17.9 ± 6.2	<.001
Total impulsivity	63.5 ± 21.8	44.3 ± 13.4	<.001

(mean ± SD: 472.2 ± 272.7) compared to the control group (mean ± SD: 583.1 ± 235.2).

We tested correlations to analyse variables affecting GDNF levels in heroin addicts and have found that lower GDNF levels are associated with high impulsivity and high Hospital Anxiety and Depression Scale-Anxiety (HAD-A), Hospital Anxiety and Depression Scale-Depression (HAD-D) scores (Figure 1).

There was an inverse correlation between serum GDNF levels and both daily dosage of used heroin (gram) and duration of addiction (Table 3).

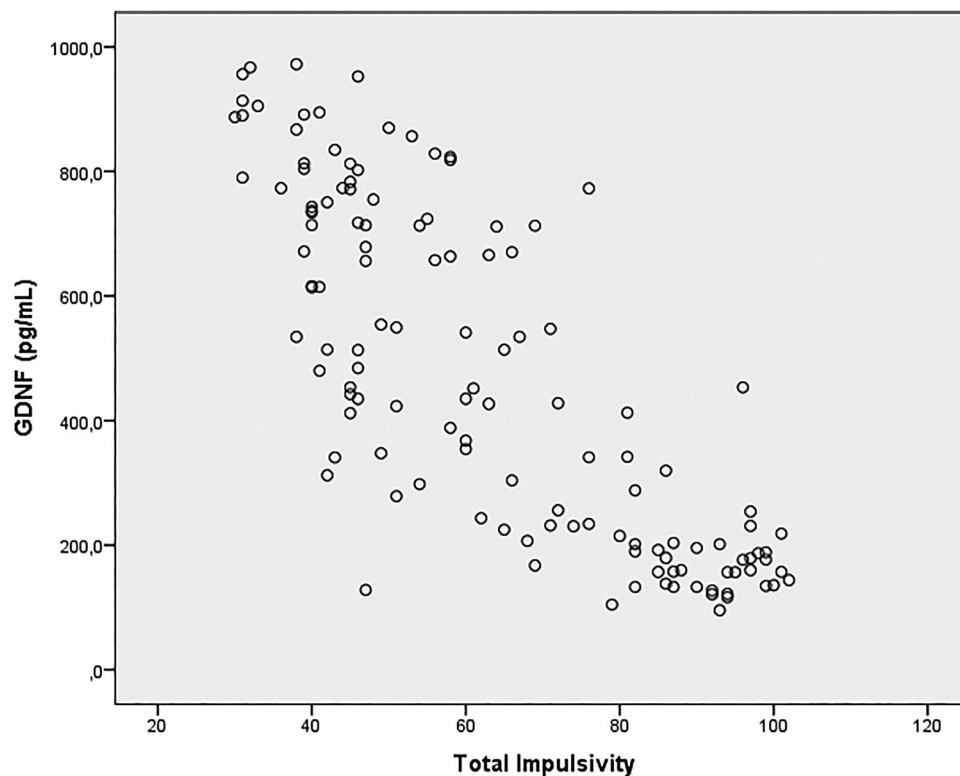


Figure 1. Correlation between GDNF levels and total impulsivity in heroin addicts.

Table 3. Variables affecting serum GDNF levels in heroin addicts.

Variables	<i>p</i>	<i>r</i>
AI	<.001	-.725
MI	<.001	-.757
UI	<.001	-.805
Total impulsivity	<.001	-.808
HAD-A	<.001	-.461
HAD-D	<.001	-.550
Heroin dosage (gram)	<.001	-.414
Duration of addiction	<.001	-.515

Discussion

GDNF plays a crucial role in maintenance and survival of adult dopamine neurons [22] and it has an important protective effect in abstinence and relapse processes of addiction.

We found that serum GDNF levels are significantly lower in heroin addicts compared to healthy controls and serum GDNF levels were inversely correlated with both daily dosage of used heroin and duration of addiction.

There is limited data about GDNF levels in heroin addicts in literature. It is found that a GDNF genotype was associated with a significantly increased risk for heroin dependence [23].

Besides, GDNF has been the subject of research for many chronic and neurodegenerative diseases. It is reported that GDNF was significantly lower in patients with Major Depressive Disorder (MDD) and Mood Disorders (MD) compared to healthy controls [24] and also patients with MD in a manic or depressive episode had lower GDNF levels compared to euthymic MD patients [25].

GDNF was found to be associated with alcohol consumption [26], addiction [27], and Parkinson's disease [28].

Kotyuk et al. reported [29] an association between a genetic variant of GDNF (rs3096140) and smoking behaviour.

In a recent study [30], it was found that GDNF regulates dopamine transporter functioning in the striatum and reducing or deleting GDNF is associated with amphetamine-induced behaviour. These data suggest endogenous GDNF plays a crucial role in addiction and many other neuropsychiatric conditions.

Besides, GDNF genes were studied in patients with schizophrenia based on the neurodevelopmental ethio-pathogenesis of the disease and it is suggested that the GDNF gene may have an involvement in the genetic liability to Schizophrenia [31].

GDNF was also found to affect synaptic and structural plasticity [32]. Future studies may focus on the role of neurotrophic factors in drug-induced synaptic plasticity changes that potentially contribute to drug abuse and addiction.

We found an association between serum GDNF levels and both daily dosage of used heroin and

duration of addiction but it is not clear that the lower levels of GDNF are a cause or result in heroin addiction.

In our study, total impulsivity scores and scores of AI, MI, and UI subscales were significantly higher in heroin addicts compared to healthy controls; and lower GDNF levels of heroin addicts were associated with increased impulsivity. We also found that lower levels of serum GDNF are associated with higher depression and anxiety scores.

It is reported that substance addicts are more impulsive [33,34], but the mechanism of this impulsivity is not clear. Our findings support the neurobiological aetiology of the impulsivity in heroin addicts.

Our study was a cross-sectional, case-control study and it cannot explain the cause-and-effect relationship between addiction and GDNF. Besides, significantly lower GDNF levels and its association with impulsivity, depression, and anxiety scores suggest a biological basis of heroin addiction and there are still many unknowns in this area.

It is reported that GDNF may facilitate or inhibit drug-taking behaviours in different pathways according to the drug type, addiction phase, and the brain site [35]. Future studies should focus on effects of GDNF in terms of different phases of addiction with neuroimaging and advanced techniques.

Conclusions

One of the main regulator growth factor, GDNF levels are significantly lower in heroin addicts. There is a significant association between serum GDNF levels and impulsivity, anxiety, and depression rates.

Neurotrophic factors such as GDNF affecting the dopaminergic system seem to find a prominent place among the target molecules in the treatment of heroin addiction.

Disclosure statement

No potential conflict of interest was reported by the authors.

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