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Hypothalamic–pituitary–adrenal axis activity in patients with pathological gambling and internet use disorder

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ABSTRACT

Alterations in secretion of stress hormones within the hypothalamic–pituitary–adrenal (HPA) axis have repeatedly been found in substance-related addictive disorders. It has been suggested that glucocorticoids might contribute to the development and maintenance of substance use disorders by facilitatory effects on behavioral responses to substances of abuse. The objective of this pilot study was to investigate HPA axis activity in patients with non-substance-related addictive disorders, i.e. pathological gambling and internet use disorder. We measured plasma levels of copeptin, a vasopressin surrogate marker, adrenocorticotropic hormone (ACTH) and cortisol in male patients with pathological gambling ($n=14$), internet use disorder ($n=11$) and matched healthy controls for pathological gambling ($n=13$) and internet use disorder ($n=10$). Plasma levels of copeptin, ACTH and cortisol in patients with pathological gambling or internet use disorder did not differ among groups. However, cortisol plasma levels correlated negatively with the severity of pathological gambling as measured by the PG-YBOCS. Together with our findings of increased serum levels of brain-derived neurotrophic factor (BDNF) in pathological gambling but not internet use disorder, these results suggest that the pathophysiology of pathological gambling shares some characteristics with substance-related addictive disorders on a neuroendocrinological level, whereas those similarities could not be observed in internet use disorder.

1. Introduction

Stress hormones influence a wide range of neuronal functions (Holsboer and Ising, 2010). In particular dysregulations of the HPA hypothalamic–pituitary–adrenal (HPA) axis have been linked to changes in emotionality (Fernández-Guasti et al., 2012; Shoener et al., 2006) and affective disorders are characterized by alterations of the HPA axis (Holsboer and Ising, 2010). Furthermore, there is growing evidence for the involvement of the HPA axis in substance-related addictive disorders and addiction-related behaviors (Nawata et al., 2012; Vinson and Brennan, 2013). Activation of the HPA axis comprises neuronal structures such as amygdala, hippocampus, and hypothalamus, which project to the paraventricular nucleus of the hypothalamus (PVN). In different regions within the PVN, magnocellular cells increase transcription of arginine vasopressin (AVP) following HPA axis activation (Angulo et al., 1991). AVP and corticotropin releasing hormone (CRH) stimulate the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, which subsequently stimulates the secretion of glucocorticoids as cortisol from the adrenal gland (Plotsky et al., 1987). The HPA axis underlies negative feedback mechanisms (Herman et al., 2012).

In mice, activation of the HPA axis, cortisol release and the consecutive negative feedback mechanism were found to be linked to cocaine-seeking behavior (Ambroggi et al., 2009). Furthermore, a non-selective CRH receptor antagonist attenuated methamphetamine-seeking behavior induced by footshock stress in rats; also, there is evidence for an anti-craving effect of selective and non-selective CRH-receptor antagonists (Nawata et al., 2012). Moreover, a persistent increase in hypothalamic AVP gene expression was found during protracted withdrawal from chronic escalating-dose cocaine in rodents (Zhou et al., 2011). Furthermore, one study found that the CRHR1 gene interacts with exposure to stressful life events and that this interaction predicted heavy alcohol consumption in adolescents (Blomeyer et al., 2013). Another study found significantly decreased serum levels of AVP as well as AVP gene alterations in alcohol-dependent patients during alcohol withdrawal (Glahn et al., 2013, 2014).

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It has been suggested that glucocorticoids contribute directly to substance dependence by facilitatory effects on behavioral responses to substances of abuse (Marinelli and Piazza, 2002; De Jong and de Kloet, 2004; Goodman, 2008; Robinson and Berridge, 1993, Robinson and Berridge, 2008; Vinson and Brennan, 2013). A recent study demonstrated interactions between HPA axis activity and dopamine release in the so-called mesolimbic reward system (Alexander et al., 2011), which is known to be involved in the development and maintenance of addictive disorders (Koob and Le Moal, 2008; Koob and Volkow, 2010). The mesolimbic pathway comprises dopaminergic neurons which project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) (Ikemoto, 2007), and has repeatedly been shown to be altered in patients with alcohol (Beck et al., 2009; Martinez et al., 2005; Wrase et al., 2002, 2007) or cocaine dependence (Asensio et al., 2010). Glucocorticoid hormones might modulate dopamine release in mesolimbic pathways via receptors in the shell region of the NAc and thereby influence the vulnerability to drugs (Marinelli and Piazza, 2002).

Pathological gambling is a condition which is primarily characterized by persistent and repetitive patterns of gambling. This behavior is often associated with impaired functioning, reduced quality of life, bankruptcy and divorce (Argo and Black, 2004; Grant and Kim, 2005). Furthermore, pathological gambling also shares some clinical and neurobiological features of substance dependence (Frascella et al., 2010), in particular alterations of the dopaminergic mesolimbic reward system (Brewer and Potenza, 2008; Grant et al., 2006). A fMRI study in patients with pathological gambling found reduced activation in the ventral striatum and the ventromedial and ventrolateral prefrontal cortex in the processing of monetary rewards during a gambling paradigm compared to healthy control subjects (Reuter et al., 2005). Those similarities suggest that pathological gambling and substance-related addictive disorders possibly share common pathophysiological mechanisms.

Internet use disorder is characterized by the inability to control internet use, which may result in impairments in daily life function (Young, 1998). At present, the disorder is not included in the ICD-10 (Dilling et al., 2013). However, in Section III of DSM-V (a section for conditions that require further research) (APA, 2013), the term "Internet Use Disorder" has been introduced and conceptualized as a behavioral addiction. Recently, the term has been modified to "Internet Gaming Disorder" (APA, 2013).

Neurobiological mechanisms in internet use disorder are still far from being understood. Neuroimaging studies in patients with internet use disorder have reported inconsistent results, indicating neural mechanisms only similar in part to addictive disorders (Ko et al., 2009). However, our pilot study focussing on neuroendocrinological alterations in pathological gambling and internet use disorder could not reveal significant differences in serum levels of the brain-derived neurotrophic factor (BDNF) in patients with internet use disorder compared to healthy controls, whereas patients with pathological gambling showed significantly enhanced BDNF serum levels (Geisel et al., 2012, 2013).

Based on findings of HPA axis alterations in substance-related addictive disorders and possible similarities in the underlying neurobiological mechanisms in substance-related and non-substance-related addictive disorders, we designed this study to investigate HPA axis activity in patients with pathological gambling and internet use disorder. To elucidate HPA axis activity at all stages, i.e. the hypothalamic, pituitary and adrenal level, we assessed plasma levels of copeptin, ACTH and cortisol in a sample of male patients suffering from pathological gambling and internet use disorder in comparison to carefully matched control subjects.

2. Material and methods

2.1. Subjects

Fourteen male patients with pathological gambling and 11 male patients with internet use disorder (see Table 1) were recruited at the outpatient unit of the Department of Psychiatry, Campus Charité Mitte, Charité – Universitätsmedizin Berlin after obtaining written informed consent. Diagnosis of pathological gambling or presence of internet use disorder was determined by an experienced psychiatrist using a semi-structured interview. All patients fulfilled diagnostic criteria for pathological gambling according to ICD-10 (Dilling et al., 2013) and DSM-IV (APA, 2000) (or criteria for internet use disorder as proposed by the DSM-V (APA, 2013). Patients suffering from comorbid axis-one diagnoses were excluded from the study, as were patients showing positive breath alcohol concentrations or patients with severe internal or neurological diseases.

Plasma concentrations of copeptin, ACTH and cortisol were measured in unmedicated patients at their first visit at the outpatient unit. The samples of healthy controls ($n=13$ for pathological gambling, $n=10$ for internet use disorder) were individually chosen to prevent confounding effects of several sociodemographic variables (Tables 1 and 2). The study was approved by the local ethics committee and adhered to the principles of the Declaration of Helsinki.

2.2. Assessments

Patients with pathological gambling were administered the Yale–Brown Obsessive–Compulsive Scale adapted for pathological gambling (PG-YBOCS), a valid and reliable measure of the severity of pathological gambling (Pallanti et al., 2005). The PG-YBOCS consists of 10 items, each rated on a 5-point severity scale from 0 to 4, and a total score ranging from 0 to 40. The first five questions assess gambling urges and thoughts, the last five assess gambling behavior.

2.3. Hormone assays

Blood samples (EDTA-containing tubes) were collected between 9 and 10 a.m. and stored at 18–25 °C until centrifugation for approximately 30 min. After centrifugation of blood samples at 5000 rpm for 5 min at 18–25 °C, aliquots were stored at −70 °C.

Table 1
Characteristics of patients with pathological gambling and healthy controls.

	Patients with pathological gambling ($n=14$)	Healthy controls ($n=13$)
Age in years	Mean=35.4, S.D.=9.5	Mean=35.2, S.D.=8.4
Sex	14 male	13 male
Smoking status	8 smokers, 6 non-smokers	7 smokers, 6 non-smokers
Urbanicity	14 urban	13 urban
Body Mass Index (BMI) in kg/m^2	Mean=27.6, S.D.=2.9	Mean=26.6, S.D.=3.2
Duration of pathological gambling in years	Mean=5.3, S.D.=5	–
Gambling frequency in hours/week	Mean=39.5, S.D.=27.1	–
Amount of indebtedness in €	Mean=28210.7, S.D.=50933.1	–
PG-YBOCS total score	Mean=17.5, S.D.=9	–
PG-YBOCS urges/thoughts score	Mean=7.4, S.D.=4.5	–
PG-YBOCS behavior score	Mean=9.8, S.D.=5.1	–
Sort of gambling	Slot-machines ($n=12$)	–
	Roulette ($n=1$)	–
	Sports bets ($n=1$)	–

Abbreviations: S.D., standard deviation. ($p>0.05$).