



HPA axis dysregulation in men with hypersexual disorder



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ABSTRACT

Hypersexual disorder integrating pathophysiological aspects such as sexual desire deregulation, sexual addiction, impulsivity and compulsivity was suggested as a diagnosis for the DSM-5. However, little is known about the neurobiology behind this disorder. A dysregulation of the hypothalamic pituitary adrenal (HPA) axis has been shown in psychiatric disorders but has not been investigated in hypersexual disorder. The aim of this study was to investigate the function of the HPA axis in hypersexual disorder.

The study includes 67 male patients with hypersexual disorder and 39 healthy male volunteers. Basal morning plasma levels of cortisol and ACTH were assessed and low dose (0.5 mg) dexamethasone suppression test was performed with cortisol and ACTH measured post dexamethasone administration. Non-suppression status was defined with DST-cortisol levels ≥ 138 nmol/l. The Sexual Compulsive scale (SCS), Hypersexual disorder current assessment scale (HD:CAS), Montgomery-Åsberg Depression Scale-self rating (MADRS-S) and Childhood trauma questionnaire (CTQ), were used for assessing hypersexual behavior, depression severity and early life adversity.

Patients with hypersexual disorder were significantly more often DST non-suppressors and had significantly higher DST-ACTH levels compared to healthy volunteers. The patients reported significantly more childhood trauma and depression symptoms compared to healthy volunteers. CTQ scores showed a significant negative correlation with DST-ACTH whereas SCS and HD:CAS scores showed a negative correlation with baseline cortisol in patients. The diagnosis of hypersexual disorder was significantly associated DST non-suppression and higher plasma DST-ACTH even when adjusted for childhood trauma.

The results suggest HPA axis dysregulation in male patients with hypersexual disorder.

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1. Introduction

Hypersexual Disorder (HD) was proposed as a diagnosis in DSM 5 and is conceptualized as a non-paraphilic sexual desire disorder with an impulsivity component. It integrates different pathophysiological perspectives such as sexual desire dysregulation, sexual addiction, impulsivity and compulsivity (Kafka, 2010), especially with mood and anxiety disorders (Kafka, 2010), and Langstrom and Hanson (2006) described that individuals with hypersexuality had more often adverse family backgrounds as well as other negative psychosocial health indicators. Moreover, childhood adversity and especially sexual abuse has been proposed to increase tendency for risky sexual behavior and hypersexuality (Aaron, 2012; Wilson and Widom, 2008). It is known that sexual behavior is under the con-

trol of central mechanisms involving neuroendocrine regulation, the limbic system and the inhibitory frontal lobe activity (Goldey and van Anders, 2012; Ragan and Martin, 2000). However, neurobiological alterations in patients with hypersexual disorder are for the moment unknown as well as basic gonadal steroid influence.

Dysregulation of the hypothalamic pituitary adrenal (HPA) axis, measured with the dexamethasone suppression test (DST) is well documented in many psychiatric disorders (Sher, 2006). Diminished suppression by dexamethasone challenge has been demonstrated in individuals suffering from severe depression, addiction and in suicide attempters (Mann, 2003) and both with diminished and enhanced suppression of plasma cortisol in individuals with childhood adversity (Newport et al., 2004).

Adversity in early-life is related to increased risk for depression, substance abuse and suicidal behavior in adulthood (Brodsky and Stanley, 2008; Jokinen et al., 2010; Teicher and Samson, 2013). Childhood adversity has developmental consequences on neurobiological systems such as the HPA axis. Heim et al. (2001) showed

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a dysregulation of the HPA axis with low basal cortisol levels in adults with a history of childhood maltreatment. This suggests that the consequences of childhood trauma may be regulated by factors related to the trauma itself such as timing and severity as well as genetic, epigenetic factors and factors of resilience (Teicher and Samson, 2013). McGowan et al. (2009) found that only suicide victims with childhood abuse had epigenetic differences in the neuron specific glucocorticoid receptor (NR3C1) promoter resulting in decreased glucocorticoid receptor expression in hippocampus suggesting that childhood trauma may modify the stress-response system permanently.

To our knowledge there are hitherto no studies of the HPA axis in hypersexual disorder. The aim of this study was to test the hypothesis that hypersexual disorder is associated with a hyperactive HPA axis in men with hypersexual disorder compared to age matched control group of healthy men taking exposure to childhood trauma into account.

2. Methods and materials

2.1. Study setting

Patients with hypersexual behavior seeking medical and/or psychotherapeutic treatment at the Center for Andrology and Sexual Medicine (CASM), at the Karolinska University Hospital as well as healthy volunteers were invited to participate in a study of biological markers for hypersexual behavior. The study protocols were approved by the Regional Ethical Review Board in Stockholm (Dnrs: 2013/1335-31/2) and the participants gave their written informed consent to the study.

2.2. Patients

This study involves 67 male patients (mean age 39.2 years, range 19–65) with hypersexual disorder included between the years 2013 and 2014 at the Center for Andrology and Sexual Medicine, (CASM), which is a multidisciplinary center for diagnostics and treatment of patients with sexual dysfunctions. Patients were recruited through advertising in media as well as referrals to the Center.

Inclusion criteria were a diagnosis of hypersexual disorder, available contact information and the age of 18 years or older. Exclusion criteria were current psychotic illness, current alcohol or drug abuse, other psychiatric disorder that would require immediate treatment such as major depression with high suicidal risk and serious physical illness such as severe hepatic or renal disease.

Hypersexual disorder was defined according to the DSM 5 proposed criteria for hypersexual disorder by Kafka (2010). These criteria include the presence of the, recurrent and intense sexual fantasies, sexual urges, or sexual behaviors in association with 4 or more of the following 5 criteria over a period of at least 6 months:

1. Time consumed by sexual fantasies, urges or behaviors repetitively interferes with other important (non-sexual) goals, activities and obligations,
2. Repetitively engaging in sexual fantasies, urges or behaviors in response to dysphoric mood states (e.g., anxiety, depression, boredom, irritability),
3. Repetitively engaging in sexual fantasies, urges or behaviors in response to stressful life events,
4. Repetitive but unsuccessful efforts to control or significantly reduce these sexual fantasies, urges or behaviors,
5. Repetitively engaging in sexual behaviors while disregarding the risk for physical or emotional harm to self or others.

Furthermore, clinically significant personal distress or impairment in social, occupational or other important areas of functioning associated with the frequency and intensity of these sexual fantasies, urges or behaviors.

Finally, these sexual fantasies, urges or behaviors are not due to the direct physiological effect of an exogenous substance (e.g., a drug of abuse or a medication). There are also the following specifiers: masturbation, pornography, sexual behavior with consenting adults, cybersex, telephone sex, strip clubs or other.

The patients were after initial contact with the study coordinators asked to log into a web based platform, leave their preliminary informed consent to participate in the study, and complete their personal information as well as the self-rated questionnaires. Subsequently, all patients were evaluated in a face to face interview by a trained psychiatrist and a psychologist using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) to establish psychiatric diagnoses and the diagnosis of hypersexual disorder. According to the inclusion and exclusion criteria eligible patients were enrolled after signing a final written informed consent.

2.3. Healthy volunteers

Forty male healthy volunteers were recruited from the Karolinska Trial Alliance (KTA) database. KTA is a support unit founded by Stockholm County Council and the Karolinska Institutet and functions as a Clinical Research Center at Karolinska University Hospital. After telephone pre-screening the volunteers gave their informed consent and were included if they were physically healthy with no serious illnesses, no previous or ongoing psychiatric illness, no first degree relative with schizophrenia, bipolar disorder or completed suicide and no previous exposure to serious trauma (assault, natural disasters that required treatment or caused disability). The healthy volunteers like the patients after initial contact with the study coordinators were asked to log into the Web based platform, leave their preliminary informed consent to participate in the study, and complete their personal information as well as the self-rated questionnaires. Individuals screened positive for pedophilic disorder were also excluded. Written informed consent was given before the baseline blood samples were taken. One individual was excluded, due to medical illness that was withheld in the pre-screening but was evident from laboratory results. The total number of healthy volunteers was thirty nine ($n = 39$). An effort was made to match the group of healthy volunteers to our patients regarding age. Possible seasonal variations were minimised by matching time of blood sampling to either spring or fall. The mean age of the healthy volunteers was 37.5 years (age range: 21–62).

2.4. Assessments

The *Mini-International Neuropsychiatric Interview* (MINI 6.0) is a validated, structured diagnostic clinical interview for assessing psychopathology along the Axis I (Sheehan et al., 1998).

The following self-rated scales were administered by the Web based platform.

Hypersexual disorder screening inventory (HDSI) consists of 7 items following the criteria (5A and 2B criteria) of hypersexual disorder. These are graded 0–4, from “never true” to “almost always true” during the past 6 months, total score ranges from 0 to 28. For a possible diagnosis of Hypersexual Disorder a minimum score of 3 is required on 4 out of 5 A-criteria, and 3 or 4 points on a minimum of 1 B-criteria is required with minimum total score of 15 (www.dsm5.org).

The *Sexual Compulsivity Scale* (SCS) is a 10-item measure where respondents endorse agreement with statements about sexually

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