Current Addiction Reports (2022) 9:23–31
https://doi.org/10.1007/s40429-021-00403-6

SEX ADDICTION (G BLYCKER AND G MESTRE-BACH, SECTION EDITORS)

Neurochemical and Hormonal Contributors to Compulsive Sexual Behavior Disorder

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Accepted: 21 November 2021 / Published online: 6 January 2022

Abstract

Purpose of Review Compulsive sexual behavior disorder has been recently included in the 11th revision of the International Classification of Diseases (ICD-11), and the possible contribution of neurochemical and hormonal factors have been reported. However, relatively little is known concerning the neurobiology underlying this disorder. The aim of this article is to review and discuss published findings in the area.

Recent Findings Evidence suggests that the neuroendocrine systems are involved in the pathophysiology of compulsive sexual behavior. The hypothalamus-pituitary adrenal axis, the hypothalamus-pituitary–gonadal axis, and the oxytocinergic system have been implicated.

Summary Further studies are needed to elucidate the exact involvement of neuroendocrine and hormonal systems in compulsive sexual behavior disorder. Prospective longitudinal studies are particularly needed, especially those considering co-occurring psychiatric disorders and obtaining hormonal assessments in experimental circumstances with appropriate control groups.

Keywords Compulsive sexual behavior disorder · Hypersexuality · Sexual addiction · HPG axis · HPA axis · Oxytocin

Introduction

Human sexual behavior is complicated, essential from an evolutionary aspect, and is closely related to both physical and mental health. There is a bidirectional relationship between psychiatric symptoms, psychiatric disorders, and sexual symptoms [1]. Indeed, sexual symptoms such as low sexual drive might be a symptom of depression, whereas high sexual engagement could reflect hypomanic or manic behavior. Moreover, Grant et al. reported that 24.9% of 293 individuals with a primary diagnosis of obsessive–compulsive disorder (OCD) experienced sexual obsessions; however, individuals with and without sexual obsessions demonstrated similar quality of life and social functioning [2]. People with Parkinson's disease also may exhibit hypersexual behavior when treated with dopamine agonists [3].

The conceptualization of hypersexuality as a distinct entity has been a matter of debate [1, 4, 5]. Different conceptual models have been proposed such as compulsive sexual behavior, sexual addiction, sexual impulsivity, and sexual desire dysregulation [1, 6, 7].

In 2010, the term "hypersexual disorder" (HD) was proposed by Kafka [1] as a potential diagnosis to be included in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5) [1]. Kafka defined HD as a nonparaphilic sexual desire disorder including features of impulsivity, sexual desire dysregulation, sexual addiction,

This article is part of the Topical Collection on *Sex Addiction*

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and compulsivity. This proposed disorder was considered to be a maladaptive response to dysphoric affective states and life stressors. Although the proposed criteria were evaluated and showed high validity and reliability [8], the diagnosis was not included in the DSM-5. However, a related condition, compulsive sexual behavior disorder (CSBD), was included in the 11th revision of the International Classification of Diseases (ICD-11) [9]. The CSBD criteria include a persistent pattern of failure to control intense, repetitive sexual impulses or urges, resulting in repetitive sexual behavior over an extended period of time. The disorder is associated with marked distress or impairment in important areas of functioning such as personal, family, social, educational, and occupational. In addition, the person may have made numerous unsuccessful efforts to reduce or to control the repetitive sexual behavior and the person continues the repetitive sexual behavior regardless of adverse consequences such as repeated relationship disruption, occupational consequences, and negative impact on health. Finally, the person persists with the sexual behavior even when no or minimal satisfaction is derived from [10].

CSBD frequently co-occurs with mood, anxiety, substance use, and impulse control disorders [7, 8, 11–13]. Although there are methodological issues and ongoing debate [14, 15] regarding the validity as well as the diagnostic criteria, CSBD seems to affect predominately men compared to women, with reported rates between 3 and 6% of the population [1, 13, 16]. By contrast, and in support of CSBD as a separate entity, evidence suggests that women are as likely as men to report sexual obsessions in OCD [2]. The debate regarding the conceptualization of CSBD is ongoing and hopefully, the inclusion of CSBD in the ICD-11 will promote more research in elucidating the phenomenology and pathophysiology of the disorder [9].

Neurobiology, Neurochemical, and Hormonal Contributions

Although many cultural and societal factors may influence human sexual behavior, biological systems have a key role and are essential to understanding sexual behavior. Biological systems involved in human sexual behavior include limbic, cortical, and neuroendocrine systems [17–19]. From a physiological perspective, sexual response is controlled by monoamines (such as noradrenaline, dopamine, and serotonin), acetylcholine, neuropeptides, glutamate, and GABA [20–23]. In addition, endocrine diseases such as hypogonadism, hyperprolactinemia, and extragonadal endocrinopathies may impact sexual function [24]. Brain lesions especially in frontal and temporal lobes as well as in the Kluver-Bucy syndrome have been linked to hypersexual behavior [13]. Regarding neuroendocrine systems and sexual behavior, much research has focused on reduced sexual behavior such as in the case of hypogonadism, linked to hypoactive sexual desire and erectile dysfunction, with only limited research on hypersexuality [24]. Recent efforts have started to elucidate different pathophysiological aspects of CSBD, mainly through neuroimaging studies [25].

Precise pathophysiological mechanisms, including underlying CSBD and neurochemical alternations, remain largely unknown. In this short review, we aim to present and discuss the most relevant studies that focus on endocrine systems involved in CSBD, especially those exploring the hypothalamus-pituitary adrenal (HPA) and hypothalamus-pituitary–gonadal (HPG) axes and the oxytocinergic system.

HPA Axis

Dysregulation of the HPA axis, evidenced by the dexamethasone suppression test (DST), has been linked to suicidality and reported in different psychiatric disorders including depression and addiction [26]. Poor regulation of stress involving the HPA axis contributes to addictions. More specifically, the corticotropin-releasing factor (CRF) is involved with increased adrenocorticotropic hormone (ACTH) levels; thus a hyperactive HPA axis may result from prolonged drug use and consequent drug withdrawal [27, 28]. This new, allostatic state is critical to induce craving and relapse.

Earlier research on the stress system and sexual behavior has reported mixed results with studies suggesting both an inhibitory and facilitating role for cortisol on sexual behavior [17]. The majority of previous studies investigated changes of the HPA axis as a result of sexual behavior. It was reported that plasma cortisol levels were both unaffected during film-induced sexual arousal as well as during sexual arousal and orgasm in healthy volunteers [29, 30]. Later studies revealed a positive correlation between baseline salivary cortisol and sexual arousal, using an imagined sexual social situation exercise in healthy volunteers [17]. Nevertheless, there was no change in salivary cortisol due to sexual thoughts when compared to control conditions. Moreover, higher salivary cortisol reactivity was reported in participants with risk-taking sexual behavior using the Trier Social Stress Test [31]. However, the possible long-standing effects of hypersexual behavior on the function of the HPA axis were not investigated in these studies.

HPA axis was not explicitly investigated in CSBD until recently when we reported for the first time that DST non-suppression status was significantly more prevalent in men with HD compared to healthy volunteers. In fact, hypersexual men had significantly higher DST ACTH plasma levels compared to healthy age-matched controls. In addition, hypersexual symptoms were inversely correlated with baseline cortisol plasma levels as well as with DST cortisol levels [32••].

Possible confounders when investigating the HPA axis include psychiatric disorders such as depression and post-traumatic stress disorder (PTSD) and childhood adversity. Furthermore, hyperactivity of the HPA axis, shown through the dexamethasone non-suppression, has been related to severe melancholic depression with psychotic symptoms and suicide attempters [33–35]. Likewise, childhood adversity, especially sexual abuse, has been proposed to increase tendency for risky sexual behavior and CSBD [36, 37] and may have detrimental effects including psychopathology in adulthood. A suggested mechanism is through dysregulation of neurobiological systems such as the HPA axis, mediated through epigenetic changes such as DNA methylation [38–40]. Importantly, in our study, the results on the HPA axis were neither related to childhood adversity nor depressive symptoms [32••].

The same cohort of men with HD was further investigated in comparing epigenetic profiles in affected and control subjects. In this study, we reported that hypersexuality is associated with reduced levels of DNA methylation at the cg23409074 locus located 48 base pairs upstream of the transcriptional start site of the corticotropin-releasing factor (CRH) [41••]. In addition, in an independent cohort of healthy male subjects, methylation levels at this locus was demonstrated to be significantly positively correlated with CRH gene expression levels, providing preliminary evidence that the identified methylation shift in hypersexual subjects may be associated with alterations in gene expression patterns. Moreover, cg23409074 methylation levels were significantly correlated between blood and four different brain regions, suggesting the findings observed in whole blood could be related to pathophysiological brain mechanisms. CRH has a key role in stress regulation as well as addiction [42] and mediates the negative affective responses to stress and craving during drug withdrawal [27, 28]. Chronic use of drugs may maintain a hyperactive HPA axis with increased levels of stress hormones such as ACTH. Epigenetic factors linked CRH gene expression have also been reported in heroin self-administration in animal models [43], suggesting links between CSBD and substance addictions.

HPG Axis

The hypothalamus-pituitary–gonadal (HPG) axis is directly involved in sexual behavior with testosterone being essential for maintaining a healthy sexual life. The effects of testosterone are mediated through effects on motivation, emotion cognition, and autonomic responses [19, 44]. Testosterone may act directly or through the conversion to estradiol, with each binding to their respective receptors. However, the explicit role of the HPG axis in sexual behavior is complex and the relationship between androgens and sexual behavior seems to be bidirectional [44, 45].

In physiological studies, erotic visual stimulation, orgasm frequency, and sexual anticipation have altered testosterone levels [17]. In addition, previous experiences and the context and the nature of sexual stimuli may moderate effects on testosterone levels. For example, repeated exposure and previous experience of men to pornography have modulated the association of testosterone levels with sexual interest. More prior exposure increased the association of testosterone levels with sexual interest [46]. Thus, testosterone may act as motivation enhancer when repeated exposure has led to habituation. Finally, the majority of studies investigating testosterone were designed to measure hormone levels following sexual stimulus (i.e., watching erotic films, engaging in masturbation or coitus) without investigating longer-term effects or effects after prolonged exposure to sexual behavior such in the case of CSBD [47].

Furthermore, in hypogonadism, lower testosterone has been related to less behaviors and poorer functioning. Interestingly, testosterone supplementation has been reported to enhance sexual function, and although there is some support for increased libido, results remain mixed [48].

Despite limited research, antiandrogen therapy has been common in paraphilic patients and sexual-offending individuals [49]. Thus, not surprisingly, most studies on testosterone levels in clinical populations were of sexual-offending individuals in forensic settings. However, these studies provide seemingly contradictory results [21, 50]. Additionally, a meta-analysis did not find group differences in testosterone levels in sexual-offending and non-sexual offending individuals. However, the authors report that differences might exist within subgroups of individuals, with perpetrators of child molestation demonstrating lower testosterone levels [50]. Although there is an overlap between sexual-offending individuals, patients, and those with CSBD, there are differences especially regarding antisocial and aggressive tendencies [51, 52].

Interestingly, there was no studies of CSBD in non-forensic settings until recently, when we reported that male CSBD patients did not differ in plasma testosterone levels compared with healthy volunteers [53••]. However, testosterone plasma levels and measures of compulsive sexual behavior (Sexual Compulsivity Scale (SCS) and Hypersexual Disorder: Current Assessment Scale (HD: CAS)) were positively correlated in CSBD patients. Thus, higher testosterone levels were related to more sexually compulsive behavior, sexual preoccupations, and sexually intrusive thoughts. Indeed, correlations between levels of androgens, especially testosterone and measurements of well-being, and sexual functions have been previously reported. This has also been reported with measurements of hypersexual symptoms such as SCS and HD: CAS in hypersexual patients. However, these scales and especially SCS measure specific aspects of hypersexuality, compulsive sexual symptoms such as

behavior, preoccupations, and intrusive thoughts. Moreover, it was first developed for the assessment of high-risk sexual behaviors such as high number of different sexual partners, no use of protective measures during intercourse, sexually transmitted diseases, and drugs and alcohol use prior to sex [1, 54, 55].

Luteinizing hormone (LH) acts as the key regulator of gonadal hormones. However, studies of LH, like those of testosterone, have reported mixed results with respect to sexual behavior. Arguably, most relevant are physiological studies and studies in forensic settings. A study of sexual arousal reported it had a postponing effect on the second peak of LH after the arousal and concurrently increased the height of the peak [47]. Previous studies of LH plasma levels in patients with erectile dysfunction reported lower bioactive/immunoactive LH ratios compared to healthy men. Interestingly, this was reversed after the recommencing of sexual activity [56].

Additionally, studies of sexual offending individuals' long-term recidivism reported that follicle-stimulating hormone (FSH) and LH levels positively correlated with hostility and were better predictors for recidivism than testosterone [57]. It was proposed that a dysregulation of LH is evident in a subgroup of sexual-offending individuals with poor downregulation. Further, among men with pedophilia, infusion of 100 mcg of synthetic LH-releasing hormone demonstrated greater increases in LH levels compared with that in both men with non-pedophilic paraphilias and men with no sexual disorders [58]. Of note, there was no difference in basal LH plasma levels between the groups. Arguably, the most relevant study with a comparable population to CSBD patients (i.e., non-paraphilic hypersexual men), investigated the long-acting analog of gonadotropin-releasing hormone, triptorelin [59]. The authors reported normal baseline levels of testosterone and LH [59]. In the study, the number of sexual attempts was reduced as were LH and testosterone levels after treatment. However, no control group was included.

In our study investigating the HPG axis, we found higher LH plasma levels in men with CSBD compared to those without [53••]. However, LH levels in both men with and without CSBD were within the reference range. As LH levels were in the normal range, these results should be interpreted with caution.

It is important to mention that different endocrine systems including the HPA and HPG axes interact, with the HPA axis having an inhibitory effect on LH suppression. According to the dual hormone hypothesis, the effect of testosterone on risk-taking behaviors and aggression are moderated by cortisol levels; i.e., testosterone is associated with risk taking in the presence of low cortisol [60, 61]. In the same line, as mentioned above, we reported a negative correlation between SCS and cortisol levels and a positive correlation between SCS and testosterone levels in CSBD men [32••, 53••]. There are also other factors besides stress and cortisol that might moderate associations between testosterone and sexual behavior. These factors include previous sexual experience, gender, and aspects of desire [61, 62].

Oxytocin

The neuropeptide oxytocin, involved in reproduction, prosocial, stress regulation, affiliative behavior, and addiction, has recently been reported to be involved in sexual behavior [63–67]. Regarding sexual behavior, oxytocin is involved in physiological reactions with increased release during penile erection and ejaculation [68–70]. In addition, plasma oxytocin levels were associated with orgasm intensity, and naloxone-induced inhibition of oxytocin resulted in a decrease in sexual satiety, independent of ejaculation [71–73].

Regarding hypersexual disorder/CSBD, we presented the first epigenetic study performed in a hypothesis-free and thereby unbiased approach. This study demonstrated both epigenetic and transcriptional involvement of microRNA-4456 in hypersexual disorder. In silico analyses provided preliminary evidence indicating that the identified microRNA regulates genes that are preferentially expressed in the brain and involved in the oxytocin signaling pathway, previously implicated in hypersexual disorder [74••]. Specifically, the study reports differential methylation of two CpG sites linked to MIR708 (cg18222192, hypomethylated) and MIR4456 (cg01299774, hypermethylated) in subjects with hypersexual disorder compared to that in healthy controls. MIR4456 was further demonstrated to be consistently differentially expressed in CSBD, using both univariate and multivariate analyses. Moreover, methylation levels of the cg01299774 site were inversely correlated with the expression levels of MIR4456, and there were disease state–dependent (i.e., CSBD-related) effects on the directions of the associations between methylation status and expression levels. Interestingly, cg01299774 was also hypermethylated in people with alcohol use disorder. In silico analyses suggested that the targets of MIR4456 include genes expressed in the hippocampus and amygdala and that are involved in the oxytocin signaling pathway.

Furthermore, preliminary data from our lab, for the first time, report higher oxytocin plasma levels in men with CSBD compared with those in healthy volunteers and that oxytocin levels are significantly positively correlated with CSBD symptom severity. This study was longitudinal, and CSBD patients exhibited a significant reduction in their oxytocin levels after following a manual-based group-administered cognitive behavioral therapy (CBT) program. In fact, the difference in oxytocin

levels was significantly positively correlated with changes in compulsive sexuality symptom severity.

The results regarding the oxytocinergic system can be interpreted through oxytocin's inhibitory role on the activity of the HPA axis during exposure to stress. It was previously reported that the transcription of CRF is regulated by oxytocin receptor activity [75]. External oxytocin administration may reduce the cortisol response to stressful stimuli [76, 77]. Oxytocin is also involved in some addiction models, reducing drug-seeking behavior and craving, effects purportedly driven by the actions of CRF [78, 79]. In addition, reported increased levels of oxytocin are in line with our previous findings of HPA axis dysregulation in men with CSBD [32••]. An alternative explanation would be the association of oxytocin and vasopressin in the regulation of impulsivity and pair bonding. Indeed, genetic variation of the oxytocin receptor gene was found to be important in pair-bonding in women [80, 81] and associated with borderline personality disorder [82, 83], a disorder characterized by severe impulsivity dysregulation.

Other Systems

There are also other neurobiological systems that are implicated in the regulation of sexual behavior and possibly CSBD. The inhibitory effects of prolactin on sexual behavior are well described [24, 63] and are proposed to result from low testosterone due to inhibition of gonadotropin secretion and low central dopamine as an indirect effect of hyperprolactinemia [24]. In addition, the cannabinoid system has gathered attention, and important interactions to key endocrine pathways, such as the HPG and HPA axes, have been reported [84–86]. Although arguably with contradictory results, the endocannabinoid system interacts with hormones such as estrogen in complex ways, inhibiting certain motivational processes including sexual desire. Thus, the endocannabinoid system exerts an inhibitory effect on the HPG axis. Additionally, cannabinoid agonists may interfere with social and sexual motivation [84].

Another potentially promising target is the opioid system. It is reported that patients on opioid maintenance therapy report negative effects on their sexuality, most commonly hypoactive sexual desire and low libido [87]. Regarding symptoms of CSBD, there were previous reports that an opioid receptor antagonist, naltrexone, might reduce urges and behaviors related with compulsive sexuality [88, 89]. Additional support comes from an open, pilot, feasibility study of 20 men with CSBD, finding a significant decrease on CSBD symptoms during treatment with naltrexone [90•].

Conclusion

We have presented recent findings regarding the involvement of key neuroendocrine systems including the HPA axis, the HPG axis, and the oxytocinergic system in CSBD. Although there are promising preliminary findings, the explicit involvement of these systems is far from elucidated. The inclusion of CSBD in the ICD-11 should help international research efforts both in diagnosis and treatment standardization as well as to provide more information on the pathophysiology of the disorder. Prospective case control studies in well-characterized CSBD patients, in both males and females, taking into account prior and current considerations such as substance use, obsessive–compulsive, and depressive disorders, PTSD, ADHD, history of childhood adversity, and sexual activity. Although forensic populations can be of great value, these should be well characterized to avoid possible confounders.

The evaluation and assessment of neurobiological correlates of CSBD should be done with caution. There are different features that might be important in the interpretation of results, most importantly as there is no definite consensus regarding the definition and phenomenology of the disorder. When investigating neurobiological systems, considering possible interactions between different neurobiological systems such as the HPA and HPG axes and the oxytocinergic system is important. Physiological variation should be taken into account, as well as the possible effect of sexual behavior on hormone levels. Regarding genetic and epigenetic studies, ideally these should include functional outcomes such as gene expression and hormone levels. Finally, the research domain criteria framework should be applied in imaging, molecular, genetic, and epigenetic studies to elucidate the pathophysiology of CSBD.

Ethics Approval

All reported studies/experiments with human or animal subjects performed by the authors have been previously published (except abovementioned preliminary data on oxytocin) and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Funding Open access funding provided by Umea University.

Declarations

Conflict of Interest The authors declare no competing interests.

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Papers of particular interest, published recently, have been highlighted as:
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•• Of major importance

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