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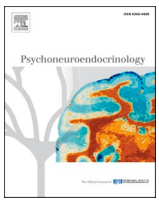

The influence of opioid blockage on the sexual response cycle: A randomized placebo-controlled experiment with relevance for the treatment of Compulsive Sexual Behavior Disorder (CSBD)

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ABSTRACT

The use of opioid antagonists is discussed as a feasible and tolerable treatment of Compulsive Sexual Behavior Disorder (CSBD). However, little is known about the influence of opioid blockage on relevant physiological functions such as sexual arousal, pain perception as well as disgust sensitivity during the sexual response cycle (SRC). Healthy participants (N = 64, n = 32 women) were invited to the laboratory twice using a double-blind, randomized cross-over design, with an interval of four weeks between sessions. Participants were randomly subjected to an SRC condition (including an erotic audio play and masturbation to orgasm) and a control condition. Participants received either naltrexone (50 mg, n = 32) or placebo at both sessions. Self-reported sexual arousal and physiological measures of arousal as well as pain perception, odor disgust sensitivity, and prolactin levels were assessed along the SRC. Naltrexone increased prolactin levels and blunted the orgasm-induced prolactin rise. Naltrexone also reduced self-reported sexual arousal throughout the sexual response cycle and blunted respiration rate during masturbation. However, naltrexone did not affect other markers of physiological arousal, pressure pain ratings and odor disgust sensitivity. These findings suggest that naltrexone has an acute negative effect on sexual arousal. Since prolactin levels mediate sexual satiation, we propose that a prolactin-induced increase in sexual satiation could explain the positive effects reported for naltrexone in the treatment of CSBD.

1. Introduction

Compulsive sexual behavior disorder (CSBD) is characterized by an inability to control repetitive sexual impulses or urges, resulting in repetitive sexual behavior, which causes problems in social and emotional functioning and marked distress (Kraus et al., 2018). It has been included in the latest revision of the ICD even though the neurobiological findings do not yet allow a clear conceptualization (Fuss et al., 2019). Many neurobiological systems are involved in the regulation of sexual behavior and interactions are complex and not fully understood yet. Likewise, knowledge of the pathophysiological background of CSBD is insufficient (Liberg et al., 2022). Still, recent studies elucidate possible underlying neuroendocrine mechanisms, suggesting a dysregulation of the hypothalamus-pituitary adrenal axis (HPA), the hypothalamus-pituitary gonadal axis (HPG) and the neurotransmitter oxytocin (Chatzittofis et al., 2016, 2020, 2022; Jokinen et al., 2017; Flanagan et al., 2022). A recent study has highlighted the feasibility and tolerability of opioid antagonists, using the opioid blocker naltrexone, in the pharmacological treatment of CSBD though randomized controlled trials are missing (Savard et al., 2020). Surprisingly, little is known about the mode of action of opioid antagonism and the influence on the sexual response cycle.

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The sexual response cycle can be assigned to two phases: The anticipatory phase, including sexual desire and motivation, and the consummatory phase, including copulation and orgasm (Argiolas, 1999). Animal research showed a dual dose-dependent effect of opioids on the sexual response cycle, meaning they facilitate the anticipatory phase and inhibit the consummatory phase (Argiolas, 1999).

In humans, likewise the use of opioid antagonists was shown to disinhibit the anticipatory phase (Sathe et al., 2001). These data suggest that opioid antagonists might have unintended side effects in people with CSBD that struggle to control their sexual urges and could (at least in the short term) also increase sexual desire and possibly the risk of sexual offenses. In contrast, other studies show a reduction of sexual deviant behavior when naltrexone was administered over a prolonged period of time (Bostwick and Bucci, 2008; Savard et al., 2020). This is in line with the successful treatment of other disorders characterized by impulsive or addictive behavior like gambling disorder, alcohol use disorder, kleptomania and binge eating disorder, where administration of opioid antagonists over several weeks had beneficial effects on symptoms (Piquet-Pessôa and Fontenelle, 2016).

Yet, the biological mechanisms by which naltrexone influences sexual behavior are not clear. One hypothesis is, that it may amplify sexual satiation and thus reduce sexual arousal and desire. Since prolactin is released immediately after an orgasm and also remains elevated for at least one hour, a mediating role of prolactin on sexual satiation was suggested (Krüger et al., 2002). In line with this, several studies have shown that chronic elevation of prolactin levels impacts sexual desire and functioning negatively (Buvat, 2003). Interestingly, opioids seem to act as prolactin-secretagogues as they decrease the inhibitory tone of tuberoinfundibular dopamine, which could be blocked by opioid antagonists (Callahan, Baumann and Rabii, 1996; Arbogast and Voogt, 1998; Kreek et al., 1999; Freeman et al., 2000; Andrews and Grattan, 2003). There are three main opioid receptor subtypes: mu-, kappa-, and delta-receptors, which are activated by endogenous or exogenous opioids and among many other physiological functions, are also involved in hormonal regulation (Waldhoer, Bartlett and Whistler, 2004). Inconsistent results exist concerning the opioid receptor subtype involved in the regulation of prolactin, with a predominant attribution to mu and kappa receptors, since corresponding receptor antagonists blocked the prolactin secretion (Callahan, Baumann and Rabii, 1996; Butelman, Harris and Kreek, 1999a, 1999b; Kreek et al., 1999; Soaje and Deis, 1999; Andrews and Grattan, 2003; Tavakoli-Nezhad and Arbogast, 2010). However, recent studies showed elevated prolactin levels in healthy subjects shortly after administration of opioid antagonists nalmefene and naltrexone, suggesting they partly act as kappa-receptor-agonists (Bart et al., 2005; Butelman et al., 2020). Naltrexone exerts its actions through mu, kappa and delta receptors, while having the highest affinity for mu receptors. Even though additional in vitro evidence for naltrexone's agonistic property exists (Wentland et al., 2009), more research is needed to support these results and to elucidate consequent effects of its action as an opioid-receptor-agonist. Beside the increase of prolactin, a disinhibitory impact on the HPA axis has been shown for naltrexone and nalmefene (Schluger et al., 1998; King et al., 2002; Al'Absi et al., 2004; Butelman et al., 2020). Several studies suggest that endogenous opioids inhibit the HPA axis and thereby explain the rise of ACTH and cortisol after administration of opioid antagonists (Delitala et al., 1994; Schluger et al., 1998; Nye et al., 1999; Grant et al., 2006). Still, due to a simultaneous increase of prolactin levels in men and women after administration of naltrexone and nalmefene (Al'Absi et al., 2004; Butelman et al., 2020), without ruling out the antagonistic effect on mu-receptors, an agonistic activity on the kappa receptor was also suggested (Butelman et al., 2020). In primates a synthetic kappa-receptor-agonist stimulated the secretion of ACTH and Cortisol, which could be blocked by a kappa-receptor-antagonist (Pascoe et al., 2008). Likewise, in rats the injection of a kappa-agonist activated the HPA axis, which was reversed by naloxone (Iyengar, Kim and Wood, 1986, 1987).

Opioid antagonism may also affect pain and disgust sensitivity, both of which are relevant for sexual behavior. Specifically, endogenous opioids have the ability to reduce pain perception, which can be prevented by opioid antagonism (Akil et al., 1984). Since endogenous opioids are released during sexual activity, pain is believed to decline through sexual arousal and orgasm. Indeed, hypoalgesia associated with sexual behavior has been shown in previous work (Whipple and Komisaruk, 1985), which may be antagonized by naltrexone. Especially for people experiencing pain during sex, opioid antagonism could thus lead to decreased sexual motivation in the long term by increasing pain perception. Furthermore, disgust sensitivity seems to be downregulated during sexual arousal (Borg and de Jong, 2012). Earlier research showed that opioid antagonism is involved in reward processing. Specifically, naltrexone increases neural activation in response to unpleasant stimuli (Murray et al., 2014). Opioid antagonism may thus elevate the sensitivity to unpleasant stimuli such as odor disgust.

In the present study, we aimed to explore how naltrexone, an opioid antagonist, affects the sexual response cycle in humans. We were interested in subjective ratings of sexual arousal, physiological levels of arousal and the influence on prolactin levels. Given that pain and disgust sensitivity may be affected by opioid antagonism, we also explored how naltrexone treatment affects both systems in a randomized placebo-controlled experiment.

2. Methods

2.1. Participants

Sixty-four healthy participants (32 male, 32 female) between the age of 18 and 50 were included in the study. They were invited to participate through a variety of means, such as an online-advert on a platform for study recruitment at the local University, posters in universities and sex-shops, and by word of mouth. Exclusion criteria were (1) any psychiatric or somatic disorders, (2) pregnancy or lactation period, (3) any drug use four weeks before inclusion, and (4) use of prescription free medication one week before inclusion, except contraceptive medication. Exclusion criteria were inquired through telephone-interviews and participants were enrolled by the study investigator. A urine drug screen was performed on the day of testing. Participants were asked to refrain from drinking and eating for at least two hours before arriving at the laboratory. Furthermore, caffeine and nicotine intake on the day of testing was prohibited. On completion of the study, participants received €100. The local ethics committee approved this study (Ärztekammer Hamburg, Germany) and the study was conducted in accordance with the good clinical practice guidelines as defined in the Declaration of Helsinki (2013).

2.2. Study design

In this study a double-blind, placebo-controlled, cross-over design was utilized. Participants were randomly assigned by a research assistant who was not involved in the study to receive either 50 mg of the opioid receptor antagonist naltrexone (Desitin Arzneimittel GmbH, Germany) (female: n = 16; male=16) or a placebo (female: n = 16; male=16). All participants were invited twice to the laboratory, with a time lag of at least 4 weeks. Each day comprised one of two different conditions. Each condition consisted of two parts. The sexual response cycle (SRC) condition was designed to induce sexual arousal without orgasm (part 1) and sexual arousal with orgasm (part 2). In part 1, participants were listening to an erotic audio play, followed by part 2, where participants were asked to masturbate to orgasm while listening to relaxing music. Part 1 of the control (CON) condition comprised listening to a neutral (non-erotic) audio play, while for part 2, participants were listening to relaxing music without masturbation (Fig. 1). Order of conditions was determined randomly. During the whole study, individuals could drink water at will.

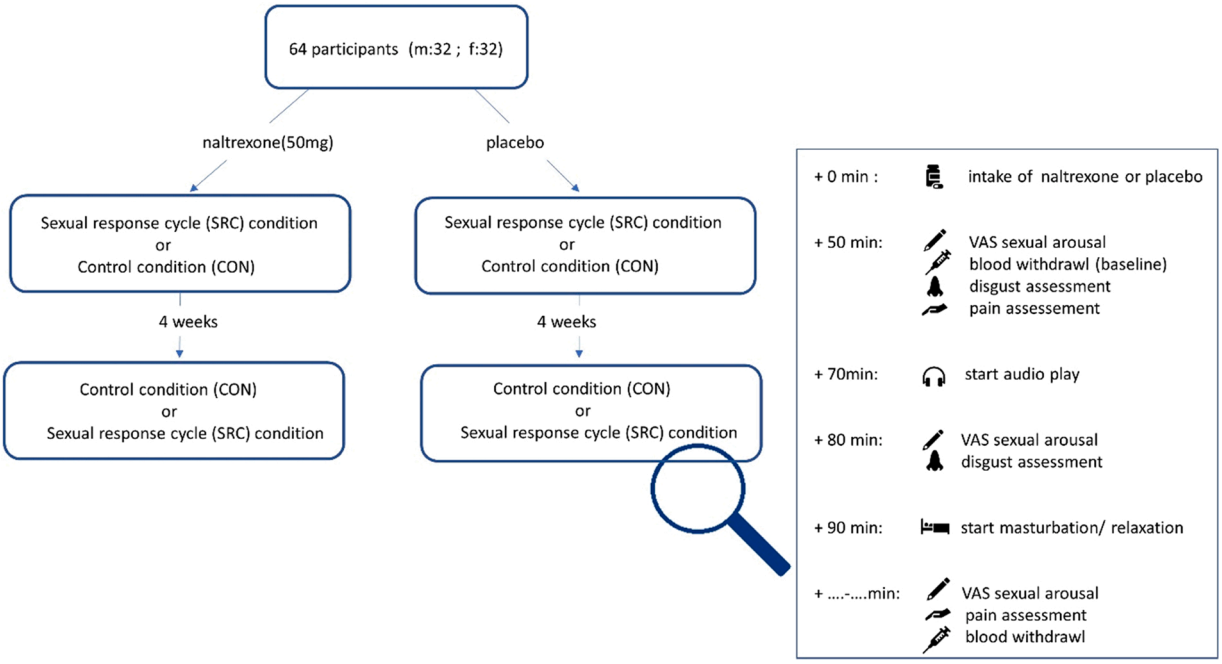

Fig. 1. Experimental timeline. Participants were invited twice to the laboratory, with a time lag of at least 4 weeks. Participants randomly received either 50 mg naltrexone or placebo. Each day comprised either the SCR or CON condition. Each condition consisted of: part 1 (erotic/non erotic audio play) and part 2 (masturbation/relaxation). Sexual arousal was reported before and after both parts. Blood collection and pain assessment were conducted before part 1 and after part 2. Disgust assessment was conducted before and after part 1.

2.3. Study procedure

Participants gave written informed consent on the first appointment. Both days began with a urine test screening for amphetamine, benzodiazepine, cocaine, morphine, methadone, and cannabinoid use (Multi-6 Drogentest, Diagnostik Nord, Germany). In case of a negative result, participants took 50 mg of naltrexone or placebo prepared by a person not involved with the study (Fig. 1). Orally administered naltrexone reaches its peak plasma concentration after 1 h (Verebey et al., 1976; Meyer et al., 1984; Ferrari et al., 1998) and has a half time ranging from approximately 4 (Meyer et al., 1984) to 10 h (Verebey et al., 1976). Until naltrexonés onset of effect, participants were asked to fill out the Sexual Desire Inventory (SDI-2) (Spector, Carey and Steinberg, 1996), the Questionnaire for assessment of disgust sensitivity (FEE) (Schienle et al., 2002) and the Sexual Excitation/Inhibition questionnaire (SESII-WM) (Velten, Scholten and Margraf, 2018) only on the first appointment. Additional information was collected through a self-developed questionnaire, including sociodemographic information about age, sex, somatic and psychiatric conditions, medication, drug consumption, sexual habits, and socioeconomic factors. Furthermore, olfactory capacity was tested with a screening test (12 Sniffn Sticks; Burghart Messtechnik GmbH, Wedel, Germany). Participants were asked about undesirable side effects, such as dry mouth, dry skin, blurred vision, dullness, nausea, vertigo, headaches, and restlessness on a 7-item scale (not existent, barely existent, existent, moderate, strong, really strong, extreme) 50 min after naltrexone- or placebo-intake on each study-day (Supplementary tables 1 and 2). Subsequently, sexual arousal was reported on a visual analogue scale (VAS) with 0 ‘no sexual arousaĺ and 100 ‘high sexual arousal’ as endpoints. Before onset of part 1, blood samples were collected, and pain perception, as well as odor disgust sensitivity were assessed through pressure stimulus to the finger and odor samples. Subsequently, participants were asked to lay down on a bed in a private room of the clinic and listened either to an erotic or non-erotic audio play for 10 min, while the investigator waited in an adjoining room. We used an erotic audio play that had been shown to reliably induce sexual arousal (Imhoff and Schmidt, 2014), while the neutral (non-erotic) audio play did not induce sexual arousal. Afterwards, current sexual arousal as well as maximal sexual arousal during the audio play were assessed again on a scale from 0 to 100. Subsequently odor disgust sensitivity was assessed a second time. Participants were then asked to lie on the bed and masturbate to orgasm while listening to relaxing music. In the control-condition, participants also listened to relaxing music but received a massage squeeze ball and were instructed to press and massage it repeatedly with their dominant hand for 10 min to imitate hand movements conducted during masturbation as reported earlier (Fuss et al., 2017). The room was only entered after receiving a signal from participants after orgasm, which was activated by turning a switch. There was no time limit for masturbation, while relaxation in the control-session ended after 10 min. Again, participants completed visual analogue scales for maximal sexual arousal during masturbation to orgasm. Five participants missed to indicate maximal sexual arousal. Blood was collected and pressure pain sensitivity was assessed a second time. At the end of the experiment, participants answered, if they had one or multiple orgasms or if they had not climaxed at all. This questionnaire was directly thrown into a mailbox to allow anonymity and achieve honest responding about whether they had an orgasm or not. In addition, participants indicated, whether they thought belonging to the medication- or placebo-group by answering ‘yes’, ‘no’ or ‘I don’t know’.

Nine participants were excluded from the data analysis after randomization because of an early termination of the study due to personal reasons (n = 6 in NAL and n = 3 in PLA group). Three participants reported no orgasm in der SRC condition and were excluded as well (n = 3 in the PLA group). Thus, our final study sample was N = 52 (n = 26 in NAL and n = 26 in PLA group; Table 1).

2.4. Blood sampling

Blood was sampled at the dominant arm two times during each investigation (before and after the respective experiment). To avoid hemolysis, stasis time was kept below one minute. For prolactin levels, blood was collected in serum tubes before the audio play and after

Table 1
Sample description: Body mass index (BMI), age, Sexual Desire Inventory (SDI-2), the Questionnaire for Assessment of disgust sensitivity (FEE), Sexual Excitation/Inhibition questionnaire (SESII-WM), Olfactory screening test (Sniffn Stix); Data are presented in mean ± standard error of the mean (SEM). Four subjects didnt fill out the SESII-WM and one subject didnt fill out the FEE.

	Placebo	Naltrexone
Participants (n)	26 (f=14, m=12)	26 (f=12, m=14)
BMI (kg/m^2)	22.97 (SEM±0.8)	22.71 (SEM±0.6)
Age (years)	28.42 (SEM±1.0)	26.73 (SEM±1.0)
SDI-2 sum score	70,38 (SEM±2.9)	76,54 (SEM±2,1)
SESII-WM sum score (Sexual Excitation)*	38,63 (SEM±1,2)	38,58 (SEM±1,1)
SESII-WM sum score (Sexual Inhibition)*	36,00 (SEM±1,5)	35,67 (SEM±1,5)
FEE sum score*	70,00 (SEM±3,9)	71,58 (SEM±5,7)
Sniffn Stix sum score	13,85 (SEM±0,2)	13,35 (SEM±0,2)

orgasm, or squeeze ball massage in the control-session. In 9 participants during SRC condition and 8 participants during CON condition blood samples were not obtained due to technical difficulties. Samples were stored at 4 °C and transported to the laboratory after blood collection. To determine prolactin levels a sandwich immunoassay (Attelica ™ IM Prolactin Test, Siemens Healthineers), that was used in previous studies (Kim et al., 2021; Park et al., 2021), was utilized. It is based on direct chemiluminescence technology and using two antibodies. The first antibody is an acridinium ester labeled goat polyclonal antibody against prolactin and the second antibody is a mouse monoclonal antibody against prolactin that is covalently bound to paramagnetic particles. This assay has an analytical sensitivity of ≤ 0,30 ng/ml (6,36 μIU/ml). Interassay CV was 5.6 % and intraassay CV 5.0 %. Based on a central 95 % interval reference intervals of 2,8–29,2 ng/ml (not pregnant women) and 2,1–17,7 ng/ml (men) were determined.

2.5. Physiological measures

Heart rate (ECG) and respiratory rate were continuously recorded during part 1 and 2 using BioNomadix wireless physiology devices and a BIOPAC MP150 data acquisition system. They were analyzed using Acqknowledge 4.4.1 software (Biopac Systems, Goleta, CA, USA). 14 respiration data (7 in NAL and 7 in PLA; 25 %) as well as 13 ECG data (7 in NAL and 6 in PLA; 23 %) had to be excluded due to poor data quality. To reduce exclusion rate, missing values due to movement artifacts were replaced with the means of nearby values if a value before and after the missing value existed.

2.6. Pressure pain threshold (PPT) and ratings (PPR)

Pressure pain was assessed using an adapted version of the Forgione-Barber pressure stimulator (Forgione and Barber, 1971; Rainwater and McNeil, 1991) before and after each experiment on the two study days. A pressure stimulus (3000 g mass) was applied for two minutes to the middle phalanx of the dominant forefinger at the first test performance and respectively on the middle finger at the second test performance of each study day to prevent augmentation of pain due to sensitization. Participants were asked to indicate first perception of pain (PPT) and pain intensity after 30 s, 60 s, 90 s, and 120 s on a visual analogue scale (PPR), ranging from 0 to 100. Following verbal descriptors were used: 20 = barely painful, 30 = very weak pain, 40 = weak pain, 50 = moderate pain, 60 = slightly strong pain, 70 = strong pain, 80 = very strong pain, 90 = nearly intolerable pain, and 100 = intolerable pain (Dagtekin et al., 2007; Koltyn et al., 2014). Three participants missed to indicate the timepoint of the first perception of pain.

2.7. Odor disgust sensitivity

Odor disgust sensitivity was assessed through odor samples. To rule out olfactory disfunction, a screening test (12 Sniffn Sticks; Burghart Messtechnik GmbH, Wedel, Germany) was performed on the first day of investigation. During each test, two odor samples were presented to the participants, holding a brown glass bottle containing the solution under the nose for 2 s. We utilized the odor sample 'Civette' (Civette Base 847; Fragrance Resources, Hamburg, Germany), which was expected to provoke disgust (feces smell) and the odor sample 'Rose' (2-Phenylethanol; Sigma-Aldrich Chemie GmbH, Munich, Germany), which was expected to be perceived as fragrant and had thus a control-function (Croy, D'Angelo and Olausson, 2014). The odor sample ´Civette´ was diluted in 1,2-Propanediol (0,1 %), while the odor sample ´Rose´ remained unadulterated, in a manner to exceed the odor threshold, without being too intense and thereby avoiding sensitization by spread of the smell (Stuck et al., 2014). Sensitization was also prevented by a time lag of 12 min between first and second test (Philpott et al., 2008), during which the second part of the session was conducted, meaning either listening to relaxing music or masturbating. Order of samples was assigned randomly and changed between first and second testing of each study day, to prevent influences on perception due to the expectation of a certain smell. Participants indicated the perception of each odor sample on a visual analogue scale ranging from − 50 'extremely unpleasant' to 50 'extremely pleasant' and the intensity, with which the smell was perceived, ranging from 0 'not intensive at all' to 100 'extremely intensive'.

2.8. Statistical analyses

Statistical analyses were carried out using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). Prolactin levels were assessed using a two-way repeated measures ANOVA with time (PRE vs. POST) x condition (SRC vs. CON) as within-subject variables and drug treatment (NAL vs. PLA) as between-subjects factor.

For assessing sexual arousal, a two-way repeated measures ANOVA with time ($t_{1–4}$) x condition (SRC vs. CON) as within-subject variables and drug treatment (NAL vs. PLA) as between-subjects factor was used.

The number of orgasms between NAL and PLA was compared using a Student's t-test.

For heart and respiration rate, a two-way repeated measures ANOVA with time (4-time intervals: 0–2 min, 2–4 min, 4–6 min, 6–8 min) x condition (SRC vs. CON) as within-subject variables and drug treatment (NAL vs. PLA) as between-subjects factor was used.

To assess odor disgust sensitivity, a repeated measures ANOVA with time (pre vs. post) x condition (SRC vs. CON) x odor (rose vs. civette) as within-subject variables and drug treatment (NAL vs. PLA) as between-subjects factor was calculated using the sum-score of the FEE as covariate. Pressure pain thresholds (PPT) were assessed using a repeated measures ANOVA with time (PRE vs. POST) x condition (SRC vs. CON) as within-subject factors and drug treatment (NAL vs. PLA) as between-subjects factor. Pressure pain ratings were assessed using a repeated measures ANOVA with time (PRE vs. POST) x condition (SRC vs. CON) x ratings (30 s, 60 s, 90 s, 120 s) as within-subject factors and drug treatment (NAL vs. PLA) as between-subjects factor.

All data are given as mean ± standard error (SEM). Statistical significance was set at $p < 0.05$, and effect sizes are given as Partial eta-squared (η_p^2) for ANOVAs.

3. Results

3.1. Naltrexone increases prolactin levels and blunts the orgasm-induced prolactin rise

Prolactin levels were higher in the NAL group compared to the PLA group at a large effect size ($F_{1,37} = 6.60$; $p = 0.014$; $\eta_p^2 = 0.151$; Fig. 2). While prolactin levels showed a pronounced increase in the PLA group following orgasm (+114 %; M_{Before} = 8.1 ± 1.1 μg/l, M_{After} = 17.3 ± 4.0 μg/l), this increase was blunted in the NAL group (+19 %; M_{Before}

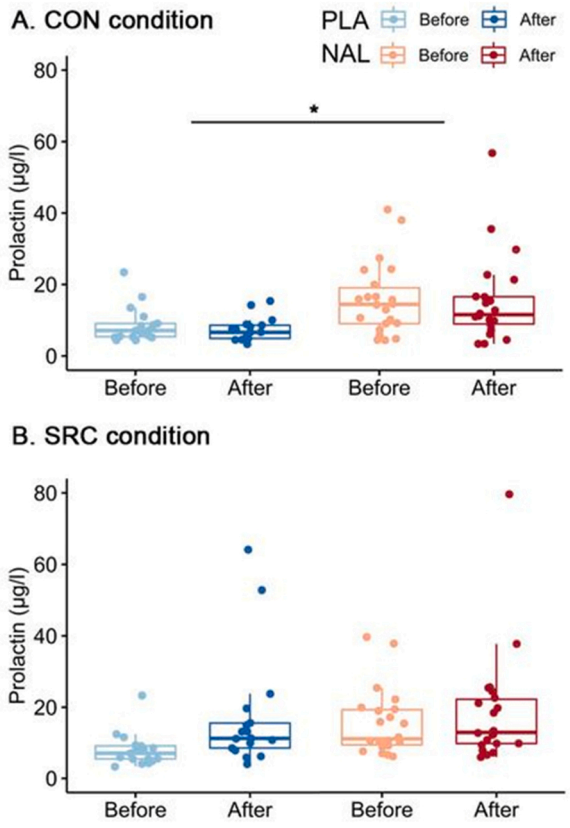

Fig. 2. Prolactin levels in the CON (A) and SRC (B) condition before and after the intervention in the PLA and NAL groups. Prolactin levels were higher in the NAL group compared to the PLA group at a large effect size ($F_{1,37} = 6.60$; $p = 0.014$; $\eta_p^2 = 0.151$; Fig. 2).

$= 15.5 \pm 2.0$ µg/l, $M_{After} = 18.5 \pm 3.4$ µg/l) where baseline levels were elevated compared to the PLA group. This difference was reflected in a significant time*condition interaction in a repeated measures ANOVA ($F_{1,37} = 7.468$; $p = 0.010$; $\eta_p^2 = 0.168$). The CON condition did not affect prolactin levels. Since previous research suggested that prolactin secretion is sexually dimorphic in a female-biased way, we performed another analysis adding "sex" of participants as an additional between-subjects factor to the model. Still, we found significantly higher prolactin levels in the NAL compared to the PLA group at a large effect size ($F_{1,35} = 7.73$; $p = 0.009$; $\eta_p^2 = 0.181$), while the effect of "sex" did not reach statistical significance ($F_{1,35} = 3.35$; $p = 0.076$; $\eta_p^2 = 0.087$) and no significant interaction was found between both factors ($F_{1,35} = 1.29$; $p = 0.28$; $\eta_p^2 = 0.033$).

3.2. Naltrexone reduces sexual arousal along the sexual response cycle

Participants were reporting their maximal sexual arousal at four time points: Before listening to the audio play (t1), during the audio play (t2), after the audio play (t3), and during masturbation/squeeze ball massage condition (t4). In the SRC condition participants reported a strong increase of maximal sexual arousal between t1 and t4 (+657 %; $M_{t1} = 10.3 \pm 2.2$; $M_{t4} = 78 \pm 3.4$), while there was a slight decrease in the CON condition (−8 %; $M_{t1} = 12.5 \pm 3.0$; $M_{t4} = 11.5 \pm 3.0$). Throughout all time points, NAL significantly reduced sexual arousal in the SRC condition with a medium effect size ($F_{1,49} = 5.915$; $p = 0.019$; $\eta_p^2 = 0.108$). This difference was particularly present during the early phases of the sexual response cycle (Fig. 3). Nevertheless, participants reported a comparable number of orgasms in both groups ($M_{PLA} = 1.1 \pm 0.1$; $M_{NAL} = 1.2 \pm 1.4$; $t = -0.63$; $df = 55$; $p = 0.53$), with most participants reporting one ($n = 51$) or two ($n = 5$) orgasms and only one participant

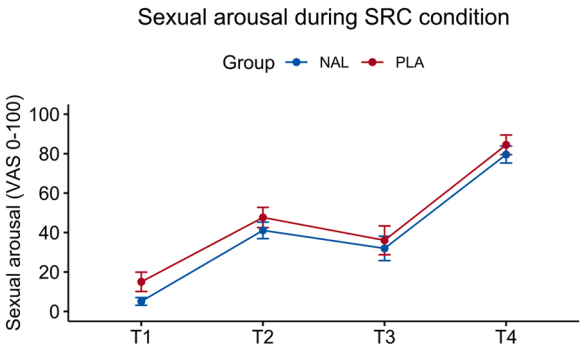

Fig. 3. Time course of effects of NAL and PLA on sexual arousal. Maximal sexual arousal was reported on a visual analogue scale (VAS) with 0 'no sexual arousal' and 100 'high sexual arousal' as endpoints at four time points: Before listening to the audio play (T1), during the audio play (T2), after the audio play (T3), and during masturbation (T4).

of the NAL group reporting 5 orgasms. Heart rate and respiration rate were descriptively higher when listening to the erotic compared to the neutral audio play (Heart rate: $F_{1126} = 3.399$; $p = 0.072$; $\eta_p^2 = 0.075$; respiration rate: $F_{1123} = 3.283$; $p = 0.077$; $\eta_p^2 = 0.074$) and increased significantly in both conditions with time (Heart rate: $F_{1126} = 9.587$; $p < 0.001$; $\eta_p^2 = 0.186$; respiration rate: $F_{1123} = 7.256$; $p < 0.001$; $\eta_p^2 = 0.150$). NAL had no effect on heart rate ($F_{1,42} = 0.382$; $p = 0.540$; $\eta_p^2 = 0.009$) and respiration rate ($F_{1,41} = 1.832$; $p = 0.183$; $\eta_p^2 = 0.043$) during listening to the audio play in both conditions.

Comparing the first 8 min of masturbation to squeeze ball massage revealed that heart rate ($F_{1105} = 15.860$; $p < 0.001$; $\eta_p^2 = 0.312$) as well as respiration rate ($F_{1105} = 4.386$; $p = 0.006$; $\eta_p^2 = 0.111$) significantly increased during masturbation but not during ball squeeze reflected by a condition*time interaction. NAL decreased respiration rate ($F_{1,35} = 3.859$; $p = 0.057$; $\eta_p^2 = 0.099$) during masturbation and ball squeeze but did not affect heart rate ($F_{1,35} = 1.121$; $p = 0.730$; $\eta_p^2 = 0.003$).

3.3. Naltrexone affects pressure pain thresholds only descriptively with a small-to-medium effect size

Pressure pain thresholds (PPT) were descriptively lower after naltrexone treatment on trend level ($F_{1,47} = 3.274$; $p = 0.077$; $\eta_p^2 = 0.065$) but did not differ between conditions and time (both $p > 0.3$). Pressure pain ratings (PPR), in contrast, were not affected by naltrexone and again time and condition had no significant effect on PPR (all $p > 0.4$). As expected, PPR increased within each trial from 30 s to 120 s ($F_{1,50} = 409.881$; $p < 0.001$; $\eta_p^2 = 0.891$).

3.4. Disgust sensitivity is not affected by naltrexone treatment

As expected, civette odor elicited higher disgust ratings compared to rose odor ($F_{1,50} = 112.308$; $p < 0.001$; $\eta_p^2 = 0.696$) and those with higher disgust sensitivity ratings in the FEE questionnaire reported higher odor disgust reflected by a significant interaction between FEE score and disgust ratings ($F_{1,50} = 4.737$; $p < 0.001$; $\eta_p^2 = 0.088$). Civette odor was also perceived more intense compared to rose odor ($F_{1,50} = 70.348$; $p < 0.001$; $\eta_p^2 = 0.589$). Interestingly, odor disgust sensitivity and perceived intensity did not differ between conditions and were not affected by naltrexone treatment (all $p > 0.4$).

4. Discussion

In the present study, we have shown that naltrexone lowers sexual arousal along the SRC and elevates prolactin levels. The relation between those two effects and their interaction with other neurohormonal systems will be discussed here, as well as the meaning of these findings for future studies. Furthermore, the role of pain and disgust will be

addressed in the context of the opioid antagonist's effect on sexual behavior.

4.1. Naltrexone, hyperprolactinemia, and sexual arousal

Our results show that prolactin levels were significantly higher in the naltrexone group under both SRC and CON condition. Interestingly this increase was not only shown after orgasm, but also before orgasm within the SRC condition. It must be considered that even though prolactin seems to be mainly controlled by an inhibiting tone through dopamine, prolactin stands under permanent influence of several neurotransmitters and its own autoregulation (Krüger et al., 2002). A negative feedback on the dopamine system in different brain areas, involved in the regulation of sexual behavior, was also suggested (Krüger et al., 2002). Elevated prolactin levels before masturbation could thereby be responsible for their blunted increase after orgasm, which was apparent in the naltrexone group (+114 %).

We have shown that elevated prolactin levels, after naltrexone intake, were associated with decreased sexual arousal along the SRC. However, the effect size was moderate and did not interfere with the course of arousal in the SRC, which was parallel in both groups. Still, our results are contradictory to the assumption that opioid antagonists might disinhibit the anticipatory phase shortly after administration (Sathe et al., 2001). They are, however, in line with studies, that show a successful use of naltrexone over a prolonged period of time in treatment of sexual deviant behavior (Bostwick and Bucci, 2008; Savard et al., 2020). Of note, the decline in sexual arousal was not as strong as expected, given the efficacy shown in those studies. Since we only included healthy subjects, these inconsistencies should be interpreted with caution, as a higher efficacy of naltrexone in patients with CSBD is possible. Furthermore, duration of naltrexone-intake could determine the extent of its negative effect on sexual desire.

So far, the treatment of CSBD with naltrexone is not sufficiently explored in clinical trials and the mode of action is not clear yet. One hypothesis is based on the interaction with rewarding processes (Bostwick and Bucci, 2008). Dopamine release is normally reinforced by endogenous opioids during orgasm and rewarding sexual behavior (Pfaus, 2009). This release seems to facilitate sexual behavior and to be responsible for sensitization of sexual desire, once sexual satiety vanishes (Pfaus, 2009). Naltrexone is expected to block the release of dopamine in the ventral tegmental area by disinhibition of GABAergic neurons during rewarding behavior (Bostwick and Bucci, 2008).

The role of prolactin in sexual satiation has been studied over the last decades (Weizman et al., 1983; Haake et al., 2002; Krüger et al., 2002; Levin, 2003; Krüger, Hartmann and Schedlowski, 2005). Neurobiological mechanisms of sexual satiation are crucial for regulatory mechanisms (Pfaus, 2009), that seem to fail in CSBD (Walton et al., 2017). Sexual arousal decreases, when the state of post-sexual satiation is achieved (Walton et al., 2017). Both chronic and acute hyperprolactinemia inhibit sexual desire and function (Krüger et al., 2002). Acute prolactin increase occurs naturally after orgasm while chronic elevation occurs through pregnancy, prolactinomas and medication (Krüger et al., 2002). In contrast to our results, the acute elevation of prolactin, caused by opioids, was blunted by opioid antagonists (Callahan, Baumann and Rabii, 1996; Arbogast and Voogt, 1998; Kreek et al., 1999; Freeman et al., 2000; Andrews and Grattan, 2003). Interestingly, recent studies showed an acute rise of prolactin-levels after the administration of opioid antagonists nalmefene and naltrexone (Bart et al., 2005; Roche and King, 2015; Butelman et al., 2020). Inconsistencies regarding opioid antagonist's effect on prolactin-levels could result from the complexity of the opioidergic and dopaminergic systems. Possible long-term effects of opioid antagonists on prolactin-release are not clear yet and should be targeted in the future. Prolactin secretion is mainly controlled by tuberoinfundibular dopamine and endogenous opioids seem to interact with corresponding neurons on the hypothalamic level (Fitzsimmons et al., 1992; Youngren et al., 1999; Tavakoli-Nezhad and Arbogast, 2010). Additionally, involvement of different opioid-receptors could play a role regarding the contradictory effects of opioids on prolactin-secretion. While kappa-receptor-agonists suppress dopamine in the mesolimbic and tuberoinfundibular system, mu-receptor-agonists likewise suppress tuberoinfundibular dopamine neurons but increase dopamine levels in the ventral tegmental area (Spanagel, Herz and Shippenberg, 1990; Andrews and Grattan, 2003). It was suggested that a partial kappa-receptor-agonism could be responsible for the prolactin increase caused by opioid antagonists nalmefene and naltrexone (Bart et al., 2005; Butelman et al., 2020). Naloxone seems to have kappa-receptor agonistic activity as well (Fukuda et al., 1998). This mechanism might also explain our findings. Likewise, it could explain contradictory results obtained in studies conducted with opioid antagonist naloxone, since naloxone seems to have a lower binding affinity to kappa receptors (Wang, Sun and Sadee, 2007). Naltrexone's affinity to kappa-receptors seems to be dose-dependent (de Laat et al., 2020).

Activation of kappa and mu-receptors by opioid-injections in the ventral tegmental area facilitates sexual behavior in rats (Mitchell and Stewart, 1990). Consequently, a partial agonism on kappa receptors in treatment of CSBD with naltrexone could be counterproductive. On the other hand, kappa-receptor activation was shown to be useful in the treatment of addiction by lowering consumption and drug seeking and could thereby also be effective in treatment of CSBD (Karkhanis, Holleran and Jones, 2017). However, labelling CSBD as an addictive behavior is still controversially discussed (Fuss et al., 2019).

4.2. Naltrexone's impact on pain & disgust

Our results show that naltrexone descriptively lowered pressure pain thresholds with a small-to-medium effect while pressure pain ratings were not affected by naltrexone. Neither PPR nor PPT differed between condition or time. Even though we could not confirm pain reduction through sexual arousal or orgasm, as previous works have pointed out (Whipple and Komisaruk, 1985), our results must be interpreted with caution, since pain assessment has occurred shortly after orgasm, when sexual arousal had already declined. Nevertheless, our results are in line with previous works, suggesting that endogenous opioids decrease pain, which could be antagonized by naltrexone (Akil et al., 1984). This could be problematic, since long-term intake could lead to painful sexual intercourse, like dyspareunia. To test this assumption genital pain assessment could be useful (Zolnoun et al., 2012). Furthermore, avoidance of sexual activity due to pain could lead to impaired sexual health, which may be interpreted as a successful treatment of CSBD if only the extent of sexual behavior is measured.

Sensory afferent pathways are closely connected to limbic areas responsible for sexual arousal (Dei et al., 1997). Although naltrexone was shown to increase neural activation in response to unpleasant stimuli (Murray et al., 2014), we did not see an impact of naltrexone on disgust sensitivity. Therefore, the decline of sexual arousal through opioid blockage, is unlikely to be traced back to elevation of disgust sensitivity. Moreover, an impact of sexual behavior on disgust sensitivity was pointed out (Borg and de Jong, 2012), while our data do not show changes in disgust ratings before and after orgasm.

4.3. Future directions

Future studies should investigate, to what extend interference with rewarding processes, sex steroids, genital pain and sexual satiation through hyperprolactinemia contribute to the decline of sex drive, caused by naltrexone.

Prolactin levels are significantly higher in the naltrexone group compared to placebo but it should be noted that the mean values do not exceed the reference levels, which is why clinical relevance should be interpreted with caution. Still, it is not clear how long-term intake of naltrexone affects prolactin levels, since corresponding trials are missing and a further rise of prolactin levels after long-term treatment cannot be

ruled out. A possible hyperprolactinemia and its side effects should be considered in future clinical trials. An induced hypogonadism, which is known to impair sexual desire (Corona et al., 2005), is conceivable. Consequently, infertility caused by a hypogonadism should be considered in treatment with opioid antagonists (Grattan and Szawka, 2019).

Interestingly, high baseline levels of sexual functioning predict a greater decline in sexual desire, caused by induced hypogonadism (Schmidt et al., 2004). Considering baseline levels of sexual behavior in patients with CSBD are expected to be above-average, this could also predict higher treatment efficacy. In line with this hypothesis, a recent study found elevated LH levels in men with Hypersexual Disorder (Chatzittofis et al., 2020).

Awareness of a possible coexistent influence on mood through sexual hormones in treatment of CSBD with naltrexone is advisable, since depressive symptoms can negatively impact sexual desire (Hintikka et al., 2009). In addition, a reduction of gonadal hormones through naltrexone could increase the risk for depression. Data concerning naltrexone's impact on depression are not sufficiently available, inconsistent and not related to CSBD treatment. Thus, depressive symptoms should be assessed in future studies.

Recently it was suggested that prolactin acts on the gonadal axis by inhibiting the hormone kisspeptin, which in turn seems to stimulate prolactin secretion, thereby creating a negative feedback-loop (Grattan and Szawka, 2019). Kisspeptin seems to be a neuromodulator in human brain processing, since it enhances brain activity in limbic and paralimbic structures in response to sexual cues and a sexual disinhibiting and rewarding role is assumed (Comninos and Dhillo, 2018). Consequently, its role in sexual disorders, especially CSBD, also regarding its interaction with endogenous opioids and their antagonists should be addressed in the future.

In addition to the HPG axis, the HPA axis also seems to be involved in the pathophysiology of CSBD. A higher rate of non-suppression in the dexamethasone suppression test was noted in men with hypersexual disorder, which may be traced back to epigenetic changes in DNA methylation (Chatzittofis et al., 2016, 2022; Jokinen et al., 2017). Likewise, oxytocin is involved in sexual behavior and was shown to be elevated in men with CSBD and to correlate positively with severity of CSBD symptoms (Flanagan et al., 2022). Previous studies demonstrated epigenetic changes in microRNA relevant for signaling of oxytocinergic pathways (Boström et al., 2020), as well as epigenetic changes correlating with levels of corticotropin-releasing hormone (CRH) (Jokinen et al., 2017). Both systems are known to interact during the reaction to stressful stimuli (Van Den Burg and Neumann, 2011). More research is needed to understand pathophysiological pathways of CSBD.

Functional brain imaging has repeatedly been used to investigate sexual behavior in humans and could be an important tool for that matter. Effects of opioids on sexual behavior seem to depend on the brain areas of opioid receptor-binding (Argiolas, 1999). More research with opioid antagonists, including brain imaging techniques is required.

4.4. Limitations

In this study we hypothesize that the increase in prolactin levels is responsible for the decrease of sexual arousal after naltrexone intake. Since we did not use a dopaminergic drug to control our results and prevent a solely correlative effect between sexual arousal and prolactin, this hypothesis should be interpreted with caution. Future studies should block the increase of prolactin to rule out a coincidental correlation between prolactin and sexual arousal.

We used the opioid antagonist naltrexone in the present study due to feasibility reasons as its oral use before masturbation seemed superior compared to intravenous application of opioid antagonists during masturbation. However, the partial kappa opioid agonism of naltrexone may have stimulated prolactin levels and this effect may not be present using other compounds such as naloxone. However, from a clinical perspective naltrexone has the advantage that it is currently used in the treatment of CSBD and the compound is currently tested in clinical trials, which makes our findings clinically relevant (Bostwick and Bucci, 2008; Savard et al., 2020). Since the opioid antagonist naloxone was shown to have a prolactin inhibitory effect, our results would have been more accurate, if we had conducted a study also using naloxone and compared its effect on sexual arousal and prolactin to those of naltrexone.

Throughout all time points (T1-T4) naltrexone significantly reduced sexual arousal in the SRC condition, but there was only a slight difference, which was particularly present during the early phases of the sexual response cycle (Fig. 3). The effect could have been stronger, if we had conducted two SRC and two control conditions for each participant and compared naltrexone's and placebo's effect for each individual.

It must be considered, that sex steroids and hormones in general might interfere with investigation of sexual behavior, since their levels vary throughout the day and along the menstrual cycle (Dei et al., 1997). For example, prolactin levels were shown to be elevated during ovulation (Capozzi et al., 2015) and different effects of naltrexone on prolactin rise in luteal and early-follicular phase of menstrual cycle were pointed out (Roche and King, 2015). To rule out unintentional interference, we assessed time-point of menstrual cycle and no differences were found between women receiving naltrexone or placebo. Furthermore, above average prolactin levels could not be assigned to the period of ovulation. Hormonal contraception was not an exclusion criterion, but there was no significant difference between number of users and type of hormonal contraception in both groups.

5. Conclusion

In conclusion, our findings demonstrate that the proposed effect of naltrexone in CSBD patients could be mediated by an acute increase of prolactin. This mechanism could induce a state of sexual satiation in which sexual desire and urges decline. Meanwhile, randomized controlled trials in patients with CSBD are yet missing. Such trials should assess how acute and chronic treatment with naltrexone affects neuroendocrinological pathways that are relevant for sexual behavior such as endogenous opioids, prolactin, kisspeptin and gonadal steroids. Furthermore, functional brain imaging and genital pain assessment could be useful tools for a better understanding of the complexity of naltrexone's interaction with human sexual behavior.

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Author contributions

N.I.: Investigation, data interpretation, original draft, review and editing. **S.V.B.:** Formal analysis, original draft, review and editing. **J.F.:** Supervision, Conceptualization, Methodology, original draft, review and editing, presentation. **L.R.:** Formal analysis, review and editing. **J. C.M.:** Resources, review and editing.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2022.105968.

References

Akil, H., et al., 1984. Endogenous opioids: biology and function. Ann. Rev. Neurosci. 7 (1), 223–255. https://doi.org/10.1146/annurev.ne.07.030184.001255.

Al'Absi, M., et al., 2004. Sex differences in pain and hypothalamic-pituitary-adrenocortical responses to opioid blockade. Psychosom. Med. 66 (2), 198–206. https://doi.org/10.1097/01.PSY.0000116250.81254.5D.

Andrews, Z.B., Grattan, D.R., 2003. Opioid receptor subtypes involved in the regulation of prolactin secretion during pregnancy and lactation. J. Neuroendocrinol. 15 (3), 227–236. https://doi.org/10.1046/J.1365-2826.2003.00975.X.

Arbogast, L.A., Voogt, J.L., 1998. Endogenous opioid peptides contribute to suckling-induced prolactin release by suppressing tyrosine hydroxylase activity and messenger ribonucleic acid levels in tuberoinfundibular dopaminergic neurons. Endocrinol. Oxf. Acad. 139 (6), 2857–2862. https://doi.org/10.1210/ENDO.139.6.6052.

Argiolas, A., 1999. Neuropeptides and sexual behaviour. Neurosci. Biobehav. Rev. 23 (8), 1127–1142. https://doi.org/10.1016/s0149-7634(99)00068-8.

Bart, G., et al., 2005. Nalmefene induced elevation in serum prolactin in normal human volunteers: partial kappa opioid agonist activity. Neuropsychopharmacology 30 (12), 2254–2262. https://doi.org/10.1038/sj.npp.1300811.

Borg, C., de Jong, P.J., 2012. Feelings of disgust and disgust-induced avoidance weaken following induced sexual arousal in women. PLoS One 7 (9), e44111. https://doi.org/10.1371/journal.pone.0044111.

Boström, A.E., et al., 2020. Hypermethylation-associated downregulation of microRNA-4456 in hypersexual disorder with putative influence on oxytocin signalling: a DNA methylation analysis of miRNA genes. Epigenetics 15 (1–2), 145–160. https://doi.org/10.1080/15592294.2019.1656157.

Bostwick, J.M., Bucci, J.A., 2008. nternet sex addiction treated with naltrexone. Mayo Clin. Proc. 83 (2), 226–230. https://doi.org/10.4065/83.2.226.

Butelman, E.R., et al., 2020. Neuroendocrine effects of naltrexone versus nalmefene in humans. Hum. Psychopharmacol. 35 (2), e2726 https://doi.org/10.1002/hup.2726.

Butelman, E.R., Harris, T.J., Kreek, M.J., 1999a. Apparent efficacy of kappa-opioid receptor ligands on serum prolactin levels in rhesus monkeys. Eur. J. Pharmacol. 383 (3), 305–309. https://doi.org/10.1016/S0014-2999(99)00640-8.

Butelman, E.R., Harris, T.J., Kreek, M.J., 1999b. Effects of E-2078, a stable dynorphin A (1-8) analog, on sedation and serum prolactin levels in rhesus monkeys. Psychopharmacology 147 (1), 73–80. https://doi.org/10.1007/S002130051144.

Buvat, J., 2003. Hyperprolactinemia and sexual function in men: a short review. Int. J. Impot. Res. 373–377. https://doi.org/10.1038/sj.ijir.3901043.

Callahan, P., Baumann, M.H., Rabii, J., 1996. Inhibition of tuberoinfundibular dopaminergic neural activity during suckling: involvement of mu and kappa opiate receptor subtypes. J. Neuroendocr. 8 (10), 771–776. https://doi.org/10.1046/J.1365-2826.1996.05207.X.

Capozzi, A., et al., 2015. Hyperprolactinemia: pathophysiology and therapeutic approach. Gynecological Endocrinology. Taylor and Francis Ltd, pp. 506–510. https://doi.org/10.3109/09513590.2015.1017810.

Chatzittofis, A., et al., 2016. HPA axis dysregulation in men with hypersexual disorder. Psychoneuroendocrinology 63, 247–253. https://doi.org/10.1016/J.PSYNEUEN.2015.10.002.

Chatzittofis, A., et al., 2020. Normal testosterone but higher luteinizing hormone plasma levels in men with hypersexual disorder. Sex. Med. 8 (2), 243–250. https://doi.org/10.1016/j.esxm.2020.02.005.

Chatzittofis, A., et al., 2022. Neurochemical and hormonal contributors to compulsive sexual behavior disorder. Curr. Addict. Rep. 9 (1), 23–31. https://doi.org/10.1007/S40429-021-00403-6.

Comninos, A.N., Dhillo, W.S., 2018. Emerging roles of Kisspeptin in sexual and emotional brain processing. Neuroendocrinology 106 (2), 195–202. https://doi.org/10.1159/000481137.

Corona, G., et al., 2005. The impotent couple: low desire. Int. J. Androl. 28 (2), 46–52. https://doi.org/10.1111/J.1365-2605.2005.00594.X.

Croy, I., D'Angelo, S., Olausson, H., 2014. Reduced pleasant touch appraisal in the presence of a disgusting odor. PLoS One 9 (3). https://doi.org/10.1371/journal.pone.0092975.

Dagtekin, O., et al., 2007. Messung der druckschmerzempfindlichkeit. Vergleich eines elektromechanisch gesteuerten algometers mit etablierten methoden. Schmerz 21 (5), 439–444. https://doi.org/10.1007/s00482-007-0544-5.

Dei, M., et al., 1997. Sex steroids and libido. Eur. J. Contracept. Reprod. Health Care 2 (4), 253–258. https://doi.org/10.3109/13625189709165303.

de Laat, B., et al., 2020. Occupancy of the kappa opioid receptor by naltrexone predicts reduction in drinking and craving. Mol. Psychiatry. https://doi.org/10.1038/s41380-020-0811-8.

Delitala, G., et al., 1994. Opioid peptide and alpha-adrenoceptor pathways in the regulation of the pituitary-adrenal axis in man. J. Endocrinol. 141 (1), 163–168. https://doi.org/10.1677/JOE.0.1410163.

Ferrari, A., et al., 1998. Serum time course of naltrexone and 6β-naltrexol levels during long term treatment in drug addicts. Drug Alcohol Depend. 52 (3), 211–220. https://doi.org/10.1016/S0376-8716(98)00098-2.

Fitzsimmons, M.D., et al., 1992. Interaction of opioid peptide-containing terminals with dopaminergic perikarya in the rat hypothalamus. Brain Res. 581 (1), 10–18. https://doi.org/10.1016/0006-8993(92)90338-A.

Flanagan, J., et al., 2022. High plasma oxytocin levels in men with hypersexual disorder. J. Clin. Endocrinol. Metab. 107 (5), E1816–E1822. https://doi.org/10.1210/CLINEM/DGAC015.

Forgione, A.G., Barber, T.X., 1971. A strain gauge pain stimulator. Psychophysiology 8 (1), 102–106. https://doi.org/10.1111/j.1469-8986.1971.tb00441.x.

Freeman, M.E., et al., 2000. Prolactin: Structure, function, and regulation of secretion. Physiological Reviews. American Physiological Society, pp. 1523–1631. https://doi.org/10.1152/physrev.2000.80.4.1523.

Fukuda, K., et al., 1998. Partial agonistic activity of naloxone on the opioid receptors expressed from complementary deoxyribonucleic acids in Chinese hamster ovary cells. Anesth. Analg. 87 (2), 450–455. https://doi.org/10.1097/00000539-199808000-00041.

Fuss, J., et al., 2017. Masturbation to orgasm stimulates the release of the endocannabinoid 2-arachidonoylglycerol in humans. J. Sex. Med. 14 (11), 1372–1379. https://doi.org/10.1016/j.jsxm.2017.09.016.

Fuss, J., et al., 2019. Compulsive sexual behavior disorder in obsessive–compulsive disorder: prevalence and associated comorbidity. J. Behav. Addict. 8 (2), 242. https://doi.org/10.1556/2006.8.2019.23.

Grant, J.E., et al., 2006. Multicenter investigation of the opioid antagonist nalmefene in the treatment of pathological gambling. Am. J. Psychiatry 163 (2), 303–312. https://doi.org/10.1176/appi.ajp.163.2.303.

Grattan, D.R., Szawka, R.E., 2019. Kisspeptin and prolactin. Semin. Reprod. Med. 93–104. https://doi.org/10.1055/s-0039-3400956.

Haake, P., et al., 2002. Absence of orgasm-induced prolactin secretion in a healthy multi-orgasmic male subject. Int. J. Impot. Res. 14 (2), 133–135. https://doi.org/10.1038/sj.ijir.3900823.

Hintikka, J., et al., 2009. Hypogonadism, decreased sexual desire, and long-term depression in middle-aged men. J. Sex. Med. 6 (7), 2049–2057. https://doi.org/10.1111/j.1743-6109.2009.01299.x.

Imhoff, R., Schmidt, A.F., 2014. Sexual disinhibition under sexual arousal: evidence for domain specificity in men and women. Arch. Sex. Behav. 43 (6), 1123–1136. https://doi.org/10.1007/s10508-014-0329-8.

Iyengar, S., Kim, H.S., Wood, P.L., 1986. Kappa opiate agonists modulate the hypothalamic-pituitary-adrenocortical axis in the rat. J. Pharmacol. Exp. Ther. 238, 2.

Iyengar, S., Kim, H.S., Wood, P.L., 1987. μ-, δ-, κ- and ϵ-Opioid receptor modulation of the hypothalamic-pituitary-adrenocortical (HPA) axis: subchronic tolerance studies of endogenous opioid peptides. Brain Res. 435 (1–2), 220–226. https://doi.org/10.1016/0006-8993(87)91604-0.

Jokinen, J., et al., 2017. Methylation of HPA axis related genes in men with hypersexual disorder. Psychoneuroendocrinology 80, 67–73. https://doi.org/10.1016/J.PSYNEUEN.2017.03.007.

Karkhanis, A., Holleran, K.M., Jones, S.R., 2017. Dynorphin/kappa opioid receptor signaling in preclinical models of alcohol, drug, and food addiction. Int. Rev. Neurobiol. 53–88. https://doi.org/10.1016/bs.irn.2017.08.001.

Kim, M.H., et al., 2021. Influence of deep neuromuscular blockade on perioperative stress response in patients undergoing robot-assisted gastrectomy: a prospective double-blinded randomized-controlled trial. J. Personal. Med. 11, 1308. https://doi.org/10.3390/JPM11121308.

King, A.C., et al., 2002. Hypothalamic-pituitary-adrenocortical (HPA) axis response and biotransformation of oral naltrexone: preliminary examination of relationship to family history of alcoholism. Neuropsychopharmacology 26 (6), 778–788. https://doi.org/10.1016/S0893-133X(01)00416-X.

Koltyn, K.F., et al., 2014. Mechanisms of exercise-induced hypoalgesia. J. Pain. 15 (12), 1294–1304. https://doi.org/10.1016/j.jpain.2014.09.006.

Kraus, S.W., et al., 2018. Compulsive sexual behaviour disorder in the ICD-11. World Psychiatry 109–110. https://doi.org/10.1002/wps.20499.

Kreek, M.J., et al., 1999. Causes elevation of serum levels of prolactin through an opioid receptor mechanism in humans: gender differences and implications for modulation of dopaminergic tone in the treatment of addictions. J. Pharmacol. Exp. Ther. 288 (*1*), 260–269.

Krüger, T.H., et al., 2002. Orgasm-induced prolactin secretion: feedback control of sexual drive? Neurosci. Biobehav. Rev. 26 (1), 31–44. https://doi.org/10.1016/S0149-7634(01)00036-7.

Krüger, T.H.C., Hartmann, U., Schedlowski, M., 2005. rolactinergic and dopaminergic mechanisms underlying sexual arousal and orgasm in humans. World J. Urol. 23 (2), 130–138. https://doi.org/10.1007/s00345-004-0496-7.

Levin, R.J., 2003. Is prolactin the biological "off switch" for human sexual arousal? Sex. Relatsh. Ther. 237–243. https://doi.org/10.1080/1468199031000099488.

Liberg, B., Görts-Öberg, K., Jokinen, J., Savard, J., Dhejne, C., Arver, S., Fuss, J., Ingvar, M., Abé, C., 2022. Neural and behavioral correlates of sexual stimuli anticipation point to addiction-like mechanisms in compulsive sexual behavior disorder. J. Behav. Addict. 11 (2), 520–532. https://doi.org/10.1556/2006.2022.00035.

Meyer, M.C., et al., 1984. Bioequivalence, dose-proportionality, and pharmacokinetics of naltrexone after oral administration. J. Clin. Psychiatry 45 (9 Pt 2), 15–19. ⟨https://pubmed.ncbi.nlm.nih.gov/6469932/⟩.

Mitchell, J.B., Stewart, J., 1990. Facilitation of sexual behaviors in the male rat associated with Intra-VTA injections of opiates. Pharmacol. Biochem. Behav. 35 (3), 643–650. https://doi.org/10.1016/0091-3057(90)90302-X.

Murray, E., et al., 2014. Opposing neural effects of naltrexone on food reward and aversion: Implications for the treatment of obesity. Psychopharmacology 231 (22), 4323–4335. https://doi.org/10.1007/s00213-014-3573-7.

Nye, E.J., et al., 1999. The use of naloxone for investigating disorders of the hypothalamic-pituitary-adrenal axis. Endocrinol. 9 (3), 161–182. https://doi.org/10.1097/00019616-199905000-00003.

Park, J.Y., et al., 2021. Surgery is a safe, effective first-line treatment modality for noninvasive prolactinomas. Pituitary 24 (6), 955–963. https://doi.org/10.1007/S11102-021-01168-X/TABLES/4.

Pascoe, J.E., et al., 2008. Effects of mu, kappa, and delta opioid receptor agonists on the function of hypothalamic–pituitary–adrenal axis in monkeys.

Psychoneuroendocrinology 33 (4), 478. https://doi.org/10.1016/J.PSYNEUEN.2008.01.006.
Pfaus, J.G., 2009. Reviews: pathways of sexual desire. J. Sex. Med. 6 (6), 1506–1533. https://doi.org/10.1111/j.1743-6109.2009.01309.x.
Philpott, C.M., et al., 2008. Olfactory clearance: what time is needed in clinical practice. J. Laryngol. Otol. 122 (9), 912–917. https://doi.org/10.1017/S0022215107000977.
Piquet-Pessôa, M., Fontenelle, L.F., 2016. Opioid antagonists in broadly defined behavioral addictions: a narrative review. Exp. Opini. Pharmacother. 835–844. https://doi.org/10.1517/14656566.2016.1145660.
Rainwater, A.J., McNeil, D.W., 1991. Reinventing the algometer: synopsis of the literature and presentation of a reliable, inexpensive model. Behav. Res. Methods Instrum. Comput. 23 (4), 486–492. https://doi.org/10.3758/BF03209989.
Roche, D.J.O., King, A.C., 2015. ex differences in acute hormonal and subjective response to naltrexone: the impact of menstrual cycle phase. Psychoneuroendocrinology 52 (1), 59–71. https://doi.org/10.1016/j.psyneuen.2014.10.013.
Sathe, R.S., et al., 2001. Naltrexone-induced augmentation of sexual response in men. Arch. Med. Res. 32 (3), 221–226. https://doi.org/10.1016/S0188-4409(01)00279-X.
Savard, J., et al., 2020. Naltrexone in compulsive sexual behavior disorder: a feasibility study of twenty men. J. Sex. Med. 17 (8), 1544–1552. https://doi.org/10.1016/j.jsxm.2020.04.318.
Schienle, A., et al., 2002. Ein Fragebogen zur Erfassung der Ekelempfindlichkeit (FEE). Z. für Klin. Psychol. Psychother 31 (2), 110–120. https://doi.org/10.1026/0084-5345.31.2.110.
Schluger, J.H., et al., 1998. Nalmefene causes greater hypothalamic-pituitary-adrenal axis activation than naloxone in normal volunteers: implications for the treatment of alcoholism. Alcohol., Clin. Exp. Res. 22 (7), 1430–1436. https://doi.org/10.1111/J.1530-0277.1998.TB03931.X.
Schmidt, P.J., et al., 2004. The effects of pharmacologically induced hypogonadism on mood in healthy men. Arch. Gen. Psychiatry 61 (10), 997–1004. https://doi.org/10.1001/archpsyc.61.10.997.
Soaje, M., Deis, R.P., 1999. Participation of the opioid system in the regulation of prolactin secretion in androgenized rats: effect of ovarian steroids. Eur. J. Pharmacol. 371 (1), 43–49. https://doi.org/10.1016/S0014-2999(99)00152-1.
Spanagel, R., Herz, A., Shippenberg, T.S., 1990. The effects of opioid peptides on dopamine release in the nucleus accumbens: an in vivo microdialysis study. J. Neurochem. 55 (5), 1734–1740. https://doi.org/10.1111/j.1471-4159.1990.tb04963.x.
Spector, I.P., Carey, M.P., Steinberg, L., 1996. The sexual desire inventory: development, factor structure, and evidence of reliability. J. Sex. Marital Ther 22 (3), 175–190. https://doi.org/10.1080/00926239608414655.
Stuck, B.A., et al., 2014. Subjective olfactory desensitization and recovery in humans. Chem. Senses 39, 151–157. https://doi.org/10.1093/chemse/bjt064.
Tavakoli-Nezhad, M., Arbogast, L.A., 2010. Mu and kappa opioid receptor expression in the mediobasal hypothalamus and effectiveness of selective antagonists on prolactin release during lactation. Neuroscience 166 (2), 359–367. https://doi.org/10.1016/J.NEUROSCIENCE.2009.12.066.
Van Den Burg, E.H., Neumann, I.D., 2011. Bridging the gap between GPCR activation and behaviour: oxytocin and prolactin signalling in the hypothalamus. J. Mol. Neurosci. 43 (2), 200–208. https://doi.org/10.1007/S12031-010-9452-8.
Velten, J., Scholten, S., Margraf, J., 2018. Psychometric properties of the Sexual Excitation/Sexual Inhibition Inventory for Women and Men (SESII-W/M) and the Sexual Excitation Scales/Sexual Inhibition Scales short form (SIS/SES-SF) in a population-based sample in Germany. PLoS One 13 (3), e0193080. https://doi.org/10.1371/journal.pone.0193080.
Verebey, K., et al., 1976. Naltrexone: disposition, metabolism, and effects after acute and chronic dosing. Clin. Pharmacol. Ther. 20 (3), 315–328. https://doi.org/10.1002/CPT1976203315.
Waldhoer, M., Bartlett, S.E. , Whistler, J.L. , 2004. Opioid Receptors. doi: 10.1146/annurev.biochem.73.011303.073940.
Walton, M.T., et al., 2017. Hypersexuality: a critical review and Introduction to the "Sexhavior Cycle". Arch. Sex. Behav. 46 (8), 2231–2251. https://doi.org/10.1007/s10508-017-0991-8.
Wang, D., Sun, X., Sadee, W., 2007. Different effects of opioid antagonists on μ-, δ-, and κ-opioid receptors with and without agonist pretreatment. J. Pharmacol. Exp. Ther. 321 (2), 544–552. https://doi.org/10.1124/JPET.106.118810.
Weizman, A., et al., 1983. The correlation of increased serum prolactin levels with decreased sexual desire and activity in elderly men. J. Am. Geriatr. Soc. 31 (8), 485–488. https://doi.org/10.1111/j.1532-5415.1983.tb05123.x.
Wentland, M.P., et al., 2009. Syntheses of novel high affinity ligands for opioid receptors. Bioorg. Med. Chem. Lett. 19 (8), 2289. https://doi.org/10.1016/J.BMCL.2009.02.078.
Whipple, B., Komisaruk, B.R., 1985. Elevation of pain threshold by vaginal stimulation in women. Pain 21 (4), 357–367. https://doi.org/10.1016/0304-3959(85)90164-2.
Youngren, O.M., et al., 1999. An opioid pathway in the hypothalamus of the turkey that stimulates prolactin secretion. Neuroendocrinology 70 (5), 317–323. https://doi.org/10.1159/000054492.
Zolnoun, D., et al., 2012. Reliability and reproducibility of novel methodology for assessment of pressure pain sensitivity in pelvis. J. Pain 13 (9), 910–920. https://doi.org/10.1016/j.jpain.2012.06.006.