A placebo-controlled, double blind study on the effect of a dopamine antagonist (Haloperidol??) on appetitive sexual conditioning in healthy female volunteers

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Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON31192

Source
ToetsingOnline

Brief title
Dopamine and classical conditioning of sexual responses

Condition

- Other condition

Synonym
female sexual arousal disorder

Health condition

seksuele stoornissen

Research involving

Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: conditioning, dopamine, female sexual arousal, sexual response

Outcome measures

Primary outcome

Genital and subjective sexual responses to the conditional stimuli.

Secondary outcome

Skin Conductance. To determine ANS arousal to the CSs and the US, skin conductance response (SCR) will be measured continuously during the pre-conditioning, conditioning, and post-conditioning phases. Also, to provide evidence of drug *bioactivity* blood pressure will be measured before, and 3-hours after, medication administration.

Study description

Background summary

Having too little sexual desire is the most common sexual problem among women (Mercer et al., 2003; Simons & Carey, 2001). A low level of desire is usually accompanied by a low level of sexual arousal, and frequently associated with sexual dissatisfaction (Basson, 2007). Little is known about the causes of hypoactive sexual desire disorder. According to an incentive motivation view, sexual motivation is the result of the activation of a sensitive sexual response system by appropriate stimuli (Agmo, 1999). Sexual behaviour, particularly orgasm, is regarded as a rewarding event, which can reinforce learning (Agmo, 1999). The positive affect produced by sexual stimulation can become associated to environmental stimuli, and these stimuli can thereby become conditioned sexual incentives. Repeated exposure to the same stimuli

while experiencing sexual reward will enhance the strength of conditioning, and the intensity of the experienced reward will probably determine the incentive properties of the conditioned stimuli (Agmo et al 2004). In the aetiology of sexual desire disorders conditioning may play a pivotal role; low desire may be caused by a lack of association between sexually rewarding experiences and stimuli, resulting in a limited number of potential sexual incentives, and it may be caused by negative sexual experiences that changed the initial positive valence of sexual incentives into a negative one.

Dopamine is hypothesized to play a role in salience coding during associative reward learning. Dopamine signalling seems to be required to learn to associate rewards with cues that predict rewards (Schultz 1998, Schultz 2001). Changes in burst firing of dopamine neurons (Schultz 1998), and transient increases in striatal dopamine concentration (Phillips et al 2003), have been shown to correlate with behavioural adaptations during reward-learning in primates and rodents. Furthermore, the dopamine hypothesis of motivation posits that dopamine is necessary for converting a neutral stimulus into an attractive desirable stimulus that is capable of eliciting an approach response (Berridge & Robinson 1998; Ikemoto & Panksepp, 1999). According to this incentive salience hypothesis the mesolimbic dopamine system attributes incentive salience to representations of stimuli that were associated with appetitive reward (Berridge & Robinson, 1998).

Several research findings in rats indicate a role of dopamine in sexual reward processes: dopamine levels increase in response to a sexual appetitive partner, dopamine agonists promote sexual activity, and dopamine antagonists diminish appetitive sexual responses (Toates, 2006). From animal research there is also evidence for a role of dopamine in sexual reward learning. In female prairie voles, a monogamous species, oxytocin in combination with activation of the dopaminergic reward system is critical in establishing the link between a particular partner and appetitive sexual behaviour (Young and Wang, 2004). Furthermore, Lopez and Ettenberg (Lopez & Ettenberg 2000, Lopez & Ettenberg 2002) observed that a cue associated with sexual reward becomes a conditioned incentive capable of eliciting approach behavior, but that dopamine receptor antagonism (with haloperidol at moderate doses) selectively attenuates this cue-induced motivation.

In humans, recent literature suggests that a polymorphism in the dopamine D4 receptor gene may contribute to individual variation in human sexual desire and arousal, indicating that variation in dopaminergic activity may influence the incentive value of stimuli and the tendency to approach such stimuli (Ben Zion et al., 2006). In human males, we recently observed an enhancing effect of levodopa, a dopamine agonist, on psychomotor activity in response to sexual stimuli (Both et al., 2005). In addition, in studies on responses to drug cues it has been observed that the dopamine antagonist haloperidol attenuated cue elicited physiological responses (Mahler & de Wit, 2005) and the urge to use the drug (Berger et al., 1996). Dopamine*s role in learning in humans is supported by recent findings showing that learning outcome can be improved pharmacologically by administration of the dopamine precursor levodopa. Examples are faster and better vocabulary learning (Knecht et al 2004), and

increased motor training success (Floel et al., 2005). To our knowledge, to date, research in humans on dopaminergic effects on the learning of sexual reward has not been done.

Study objective

The purpose of this study is to investigate the role of dopamine in learning about sexual reward in healthy females. We suppose that repeated associations between a neutral stimulus and sexual stimulation results, through classical conditioning, in a learned appetitive sexual response to this stimulus. It is hypothesized that acute blockade of DA receptors with a dopamine antagonist (haloperidol©) will attenuate this appetitive conditioning effect due to blocking of dopamine activity.

Study design

The protocol concerns a randomised, double-blind, placebo-controlled study on the effect of a single dose of haloperidol on learning about sexual reward in healthy sexually functional female volunteers. To investigate the hypothesized critical role of dopamine in learning of sexual reward, classical conditioning of genital and subjective sexual arousal will be studied in a haloperidol condition (N=64) and in a placebo condition (N= 64) using a between subjects design. A differential conditioning paradigm will be applied, in which women, in both conditions, are presented with two neutral stimuli, CS+ and CS-, of which only the CS+ is followed by an appetitive sexual unconditional stimulus (US). Genital vibrotactile stimulation will be applied as appetitive sexual US. During a pre-conditioning, conditioning, and post-conditioning phase women will view the two neutral pictures repeatedly, while genital sexual arousal is assessed as vaginal pulse amplitude using vaginal photoplethysmography (dependent variable). Self-reported ratings of emotional valence and subjective sexual arousal (dependent variables) are collected during the pre-conditioning and post-conditioning phase. It is expected that in the placebo condition, pairing of the CS+ to the vibrotactile stimulation during the conditioning phase will result in higher genital and subjective arousal and a more positive valence of the CS+ compared to the CS- during the post-conditioning phase, and that these associative learning effects will be attenuated under the dopamine antagonist (haloperidol) condition.
To test the robustness of the experimental paradigm, first a pilot study on sexual conditioning in healthy sexually functional women that we conducted previously will be replicated. If in this replication study conditioning of sexual response is observed, the study will be extended to the placebo and haloperidol condition.

Study burden and risks

The vaginal photoplethysmograph used in this study is considered a safe device.

No harmful events have been reported. Furthermore, the device used to measure genital arousal will be sterilized before each use, according to plasma sterilization procedure. From previous studies (Both, Laan & Everared, 2007; Laan & van Lunsen, 2007) it is known that the genital vibrotactile stimulation will not cause harm or discomfort.

Based on the information provided by the clinical trial pharmacist (LUMC) serious adverse effects of a single dose of 5 mg haloperidol are not to be expected. Possible side effects of a single dose of haloperidol 5 mg are muscle-stiffness or trembling, drowsiness, dizziness, irritability, nausea, and increased heart-rate. Studies with a comparable single dose of haloperidol (4 mg) conducted by others (e.g. Mahler & de Wit, 2005; Berger, et al., 1996) report no adverse side effects of the medication.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

female, heterosexual, no sexual complaints for at least one year, and sexually active including intercourse

Exclusion criteria

- Age < 18 or > 45 years
- BMI < 19
- Homosexual orientation (because of the *male* neutral stimuli)
- Pregnancy or lactation
- A diagnosis of affective, psychotic or substance related disorder according to DSM-IV-TR
- Having undergone a hysterectomy or prolapse surgery
- Using medication that may affect sexual response. To determine possible sexual side-effects the *Farmacotherapeutisch kompas* 2007 will be used.
- Current use of psycho-pharmacological medication, or recent use (less than 4 weeks before participation) of such medication
- Disorders of the genitals that may influence the sexual response or the measurement of the response
- Using drugs or medication that may interfere with haloperidol (for example alcohol, or medication that influences the central nervous system).
- A medical, and/or psychiatric illness or disorder, or a medical, and/or psychiatric history that indicates a risk in using haloperidol (for example cardiac arrhythmia, parkinson, depression, epilepsy, thyroid disorders).
- Use of alcohol or drugs 24 hours preceding participation in the experimental session

Study design

Design

Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2007
Enrollment:	128
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Haldol
Generic name:	Haloperidol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	26-06-2007
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2007-001623-35-NL

Register	ID
CCMO	NL17463.058.07