Specificity of the neuroendocrine response to orgasm during sexual arousal in men

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Abstract

We have demonstrated that sexual activity produces transient sympathoadrenal activation and a pronounced, long-lasting increase in prolactin in men and women. However, by analyzing endocrine alterations at 10-min intervals, a precise assignment of these changes to the pre-, peri- and postorgasmic periods was not possible. Thus, the current study aimed to accurately differentiate the endocrine response to sexual arousal and orgasm in men using an automatic blood collection technique with 2-min sampling intervals. Blood was drawn continuously before, during and after orgasm over a total period of 40 min in 10 healthy subjects and were compared with samples obtained under a control condition. Sexual activity induced transient increases of plasma epinephrine and norepinephrine levels during orgasm with a rapid decline thereafter. In contrast, prolactin levels increased immediately after orgasm and remained elevated throughout the experiment. Although oxytocin was acutely increased after orgasm, these changes were not consistent and did not reach statistical significance. Vasopressin, LH, FSH and testosterone plasma concentrations remained unaltered during sexual arousal and orgasm. These data confirm that prolactin is secreted after orgasm and, compared with oxytocin, seems to represent a more reliable and sustained marker for orgasm in man. The results further reinforce a role for prolactin either as a neuroendocrine reproductive reflex or as a feedback mechanism modulating dopaminergic systems in the central nervous system that are responsible for appetitive behavior.

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Introduction

The neuroendocrine effects of sexual arousal and orgasm in humans are poorly understood. However, various medications with psycho- and somatotropic properties affect the neuroendocrine system and thereby alter sexual functions (Schiavi & Segraves 1995, Rosen *et al.* 1999, Meston & Frohlich 2000, Kandeel *et al.* 2001). For example, chronic treatment with antidepressive or antipsychotic medications may induce hyperprolactinemia because they modulate serotonergic and dopaminergic release of pituitary hormones (Breier *et al.* 1999, Hummer *et al.* 1999, Aizenberg *et al.* 2001). Specifically, typical antipsychotics and the new selective serotonin reuptake inhibitors reduce sexual arousability and function by inducing hyperprolactinemia (Haddad *et al.* 2001, Johri *et al.* 2001).

To extend the understanding of neuroendocrine mechanisms regulating sexual behavior we continuously assessed the endocrine response to sexual activity in humans. These studies revealed that sexual arousal and orgasm produced transient sympathoadrenal activation and a pronounced increase in plasma prolactin concentrations in men and women, independent of whether orgasm was induced by masturbation or coitus (Krüger *et al.* 1998, Exton *et al.* 1999). Further investigations demonstrated that increases in plasma prolactin during sexual stimulation did not occur without orgasm (Exton *et al.* 2000). Together, these studies suggested prolactin to be a specific endocrine marker of orgasm in men and women.

Nevertheless, the interpretation of these results was restricted, since continuously collected plasma samples were analyzed over 10-min intervals, therefore not allowing specific attribution of endocrine changes to the pre-, peri- or postorgasmic phase of sexual arousal. However, this attribution is of crucial interest for the interpretation of orgasm-induced endocrine changes. Particularly, postorgasmic endocrine alterations may have strong relevance for the understanding of sexual refractoriness and loss of sexual drive. Indeed, we hypothesized that an orgasm-induced increase in prolactin may represent a regulatory
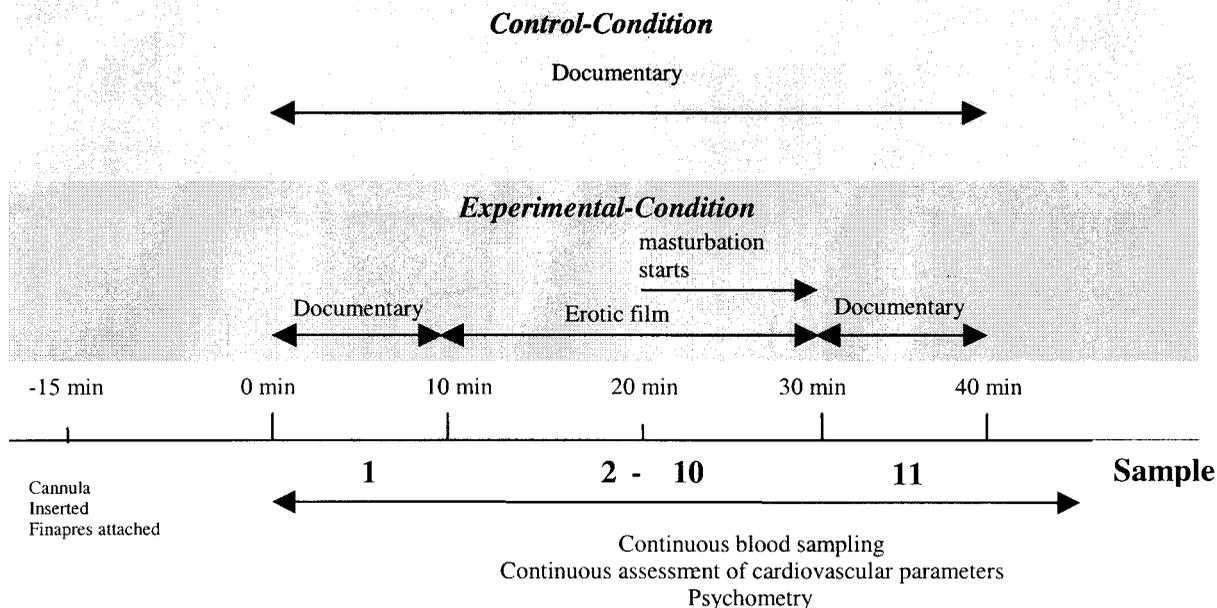
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Figure 1 Experimental paradigm. The experimental paradigm consisted of an experimental and a control session, each lasting 40 min. Each subject completed both sessions in a cross-over design, with continuous assessment of endocrine, psychometric and cardiovascular parameters throughout each session. Sample 1 represents the basal value. Samples 2 to 10 were drawn during sexual arousal and masturbation, with sample 8 representing the response to orgasm, and samples 9 and 10 the postorgasmic phase. Sample 11 was drawn 10 min after orgasm and displayed the recovery phase.

factor for reproductive function and/or a feedback mechanism that signals central nervous system (CNS) centers controlling sexual arousability (Krüger *et al.* 2002).

Therefore, in the current study we improved the technique of continuous blood sampling by dividing blood samples into 2-min intervals, allowing precise and event-related monitoring of endocrine changes during sexual arousal and orgasm. Moreover, besides examination of the sympathoadrenal and anterior pituitary system, we assessed changes in plasma oxytocin and vasopressin concentrations to compare the role of prolactin and oxytocin as reliable markers of orgasm.

Materials and Methods

Participants

Ten healthy males (mean age 25·2 ± 1·21, age range 18–30 years) participated in this study after providing written informed consent. Subjects were recruited by advertisement at the Hannover Medical School, Germany. The investigation was conducted in accordance with the guidelines proposed in The Declaration of Helsinki and has been approved by the Ethics Committee for Investigations involving human subjects at the Hannover Medical School. Participants completed a general medical/health questionnaire to exclude individuals taking medication, abusing drugs/alcohol or exhibiting endo-

crinological or psychological disorders. Additionally, a questionnaire for the evaluation of sexual problems/dysfunctions in males was employed. Furthermore, subjects were screened for psychogenic erectile dysfunction by a specific questionnaire (Bancroft & Janssen 2000). Subjects did not show any significant differences in the specific subscales (sexual inhibitory and excitatory scale) in comparison with a normative sample of healthy males.

Subjects underwent a semi-structured interview and a physical examination by a research physician. All participants were sexually active and reported having an exclusively heterosexual orientation and a relaxed attitude towards masturbation and erotic films. Subjects reported an average refractory period of 19·5 ± 2·5 min.

Design and procedure

The investigation was performed as a cross-over design with repeated measures so that each subject participated in an experimental and control condition. In the experimental sessions a documentary film was observed for 10 min, followed by 20 min of a pornographic film, and a further 10 min documentary. Following 10 min of pornographic film, subjects were asked to masturbate until orgasm. Subjects indicated the time point of orgasm by giving a signal via an electronic communication system. In the control session a documentary film was shown for 40 min (Fig. 1) (Krüger *et al.* 1998, Exton *et al.* 1999, 2000).

Experiments were conducted in a separate sound-attenuated room equipped with a reclined armchair, a color television and a video cassette player. All leads, including the blood line, passed through the wall into the adjacent room where the cardiovascular data and blood samples were collected, allowing subjects to be completely isolated throughout the entire experiment. At the beginning of the experiments subjects positioned themselves in the armchair in front of the screen. The cardiovascular monitor was then engaged 20 min prior to the film and a steady baseline reading was obtained. An i.v. cannula was inserted for continuous blood sampling, which was initiated immediately before the beginning of the film with the samples divided into 2-min intervals. Of the total samples collected over the 40-min period, particular probes were used for endocrine analysis. Specifically, sample 1 represented the basal value and was selected in the middle of the neutral stimulus. Other samples from this sequence were not used for endocrine assessment. To achieve comparability of periorgasmic changes among all subjects, the endocrine response pattern of each subject during the 20-min audiovisual erotic presentation was referenced to the time of orgasm. Following 10 min of pornographic video, orgasm occurred between the 2nd and 8th minute. Consequently, samples 2 to 4 represented the response to film-induced sexual arousal. Samples 5 to 7 reflected endocrine changes induced by sexual arousal and/or masturbation, whereby sample 7 represented the immediate preorgasmic period. Sample 8 represented the 2-min interval that included the response to orgasm, whereas the next two samples (9 and 10) reflected the immediate postorgasmic state. Finally, sample 11 was selected 10 min after orgasm and displayed the recovery phase. Other samples from this sequence were not analyzed.

Endocrine measures

For continuous blood sampling we used a commercial heparinized catheter system (ConFlo 100, Carmeda, Stockholm, Sweden), which consisted of a catheter tubing with an internal diameter of 0·8 mm and a length of 100 cm, and an i.v. cannula (20 G, Insyte-W, Carmeda, Stockholm, Sweden). The dead volume of this system was 1·2 ml. The i.v. cannula was inserted into a forearm vein of the nondominant arm and connected to the catheter tubing. The blood-line passed through the wall into the adjoining room and was driven by a small portable pump (Fresenius, Homburg, Germany) (Krüger *et al.* 1998, Exton *et al.* 1999). Blood flow was adjusted to 5 ml/min, so that approximately 10 ml blood per 2 min were collected (i.e. 200 ml per session). Blood collection of each sample was delayed by the time taken for blood to pass through the tube dead space (14 s). Blood was sampled in EDTA tubes (Sarstedt, Nümbrecht, Germany), containing aprotinin for protease inhibition (Trasylol, 500 KIU/ml

blood). Blood was immediately stored on ice until samples were centrifuged. Plasma was stored in glass aliquots at −30 °C until time of hormone assay.

All samples from the one participant were assayed in duplicate within the same assay. Catecholamine plasma levels were measured by high pressure liquid chromatography (Smedes *et al.* 1982, Ehrenreich *et al.* 1997). The intra- and interassay variabilities for norepinephrine were 6·2% and 8·0% respectively, and for epinephrine were 4·0% and 5·1% respectively. Prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone and cortisol were detected by the Automated Chemiluminescence-Immunoassay System 180 (ACS; Centaur, Chiron Diagnostics, Leverkusen, Germany). The intra- and interassay coefficients of variance were, respectively, 2·5% and 3·6% for prolactin, 2·8% and 4·6% for FSH, 4·7% and 6·3% for LH, 5·6% and 6·6% for testosterone and 4·5% and 6·4% for cortisol. To separate the peptides vasopressin and oxytocin from potentially interfering substances and to achieve a higher concentration, samples used for vasopressin determination were treated by the usual ethanol extraction procedures, whereas oxytocin was purified by Sep-pak C18/column extraction as described elsewhere (Blaicher *et al.* 1999). Vasopressin and oxytocin concentrations were evaluated by immunoradiometric assay (Euro-Diagnostica, Malmö, Sweden; Peninsula Laboratories, Belmont, CA, USA), with an intra- and interassay variability of, respectively, 4·9% and 6·9% for vasopressin and 5·1% and 7·2% for oxytocin.

Cardiovascular measures

The cardiovascular parameters, heart rate and systolic and diastolic blood pressure, were monitored continuously via a finger cuff connected to a blood pressure monitor (Finapres, Ohmeda, Louisville, USA) in the adjoining room. Cardiovascular activity was recorded every 30 s, and the heart rate and blood pressure values were averaged over 2-min intervals and analyzed in parallel with the 2-min interval blood samples.

Psychometric measures

To our knowledge, there is no standardized questionnaire for the evaluation of acute sexual experience in an experimental situation. Therefore, we designed the Acute Sexual Experience Scale (ASES), containing six subscales with 52 items (Krüger *et al.* 1998, Exton *et al.* 1999). The questionnaire evaluates different characteristics of appetitive, consummatory and refractory sexual behavior in males. Apart from control items (e.g. for evaluating the occurrence of an orgasm or the ejaculation latency), the questionnaire consists of self-reporting ratings of sexual functioning using visual analog rating scales (0–100, from 'not at all' to 'extremely'). The scales examined sexual
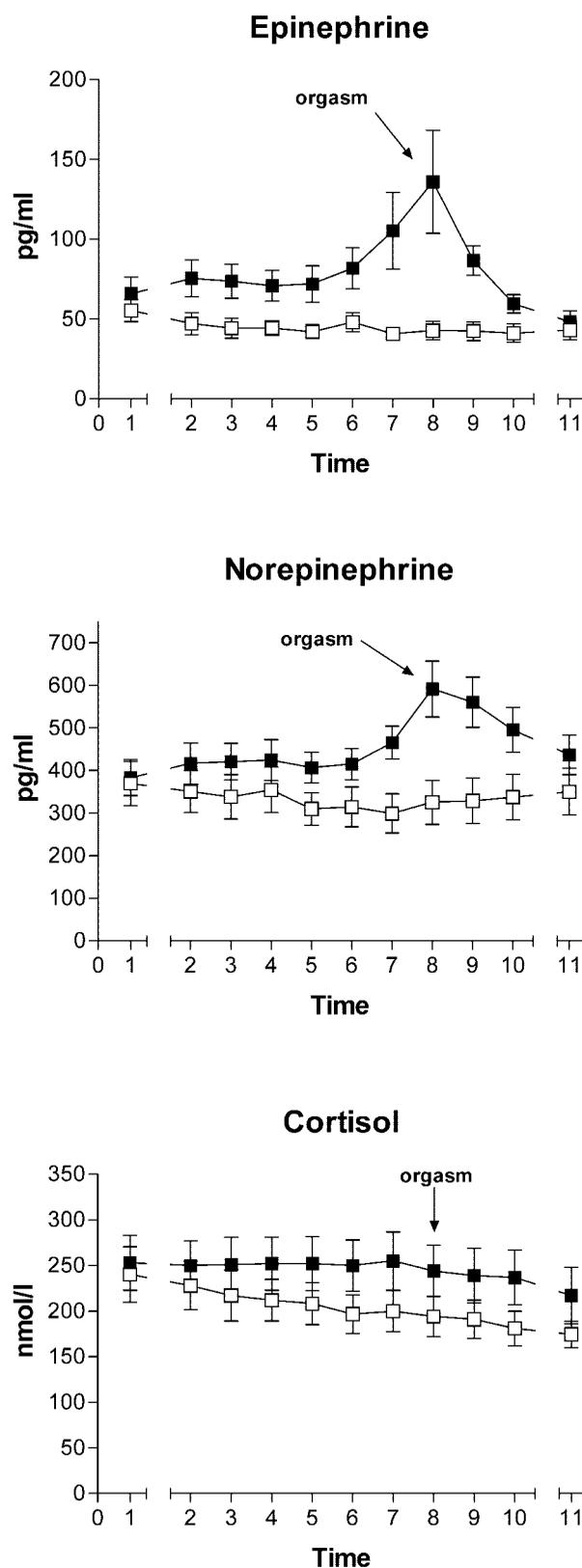
functioning both in absolute values and as compared with normally experienced sexuality in a real life situation like masturbation and sexual intercourse.

Statistical analysis

Following statistical confirmation of normal distribution and variance homogeneity, cardiovascular and endocrine data from all subjects were analyzed by two factor (condition × time) analyses of variance (ANOVA). In addition, all ANOVAs were corrected for nonsphericity using the Geisser Greenhouse method (Vasey & Thayer 1987). For each repeated measure, we report the uncorrected degrees of freedom and the epsilon corrected *P*-value. If not otherwise stated we report the condition × time effect. Post-hoc analyses were conducted via paired-comparison *t*-test, with α adjusted for multiple comparisons. An α of 0·05 was considered statistically reliable for all analyses.

Results

Analyses of psychometric measures

All subjects in the experimental condition reported having an orgasm within the second part of the pornographic sequence. The pornographic film was judged to be sexually arousing (mean=67 ± 7 mm on a 100 mm visual analog rating scale). The intensity (mean=62 ± 9) and quality of orgasm (mean=48 ± 7) were considered to be moderate and slightly below that experienced in a real life situation (mean=41 ± 5 for intensity of orgasm, and mean=38 ± 5 for quality of orgasm, measured on a 100 mm visual analogue rating scale with 0 mm representing 'much weaker' and 100 mm representing 'much stronger'). Subjects indicated less general arousal during the experimental condition compared with the control condition (F(1,8)=15·5, *P*<0·01, condition effect) (data not shown).

Analyses of cardiovascular measures

As observed in previous studies, participants revealed transient increases in heart rate, and in systolic and diastolic blood pressure during sexual arousal and orgasm (interval 2 to 8), reaching peak levels during orgasm which then declined to baseline levels (interval 9 to 11) (data not shown).

Figure 2 Plasma concentrations of epinephrine, norepinephrine, and cortisol, analyzed at 2-min intervals for the experimental (■) and control (□) condition. Sample 1 represents the basal value. Samples 2 to 10 were drawn during sexual arousal and masturbation, with sample 8 representing the orgasm and samples 9 and 10 the postorgasmic phase. Sample 11 was drawn 10 min after orgasm and displayed the recovery phase. Data are presented as means ± S.E.
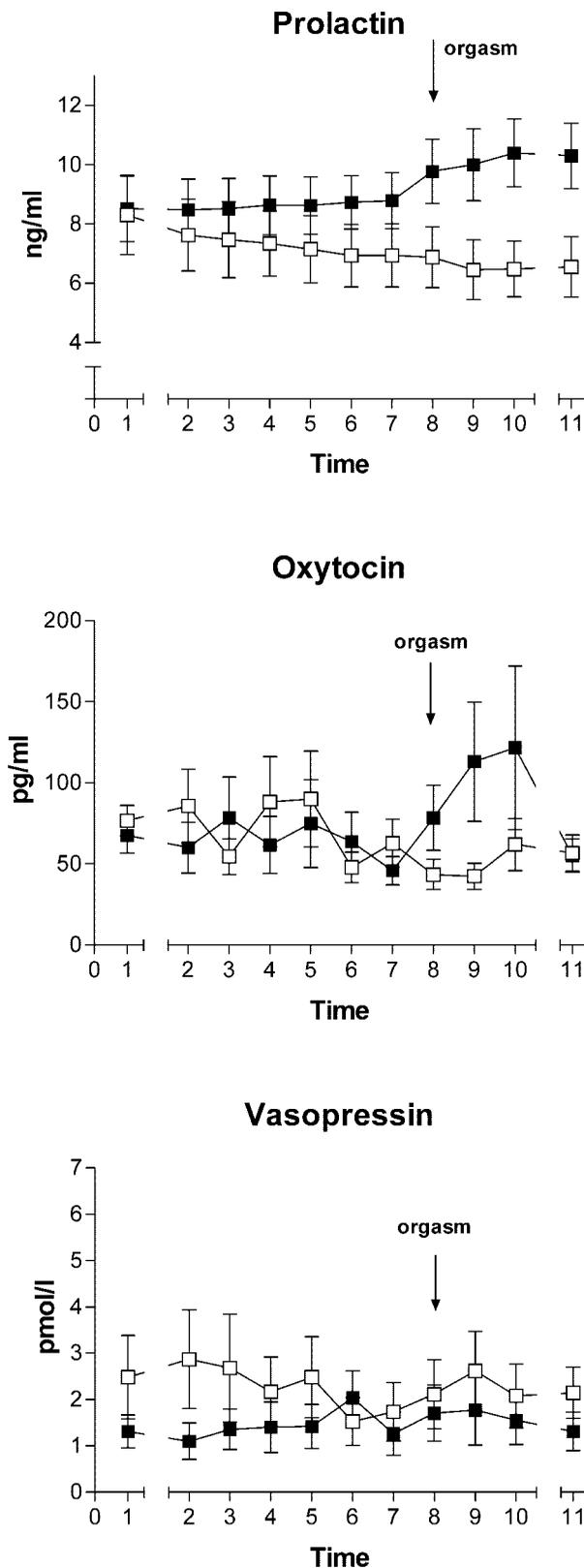
Analyses of endocrine measures

Sympathetic adrenal hormones The basal levels of epinephrine showed no difference between the control and experimental conditions at baseline. However, epinephrine increased during sexual arousal and masturbation, and peaked during orgasm (>100% increase), with an immediate postorgasmic decline to basal levels ($F_{(10,90)} = 4\cdot60$, $P<0.001$; Fig. 2). Similarly, basal norepinephrine levels did not differ during the neutral stimulus. There was a slight increase during sexual arousal and masturbation with a significant increase during orgasm ($F_{(10,90)} = 5\cdot12$, $P<0.001$; Fig. 2). Norepinephrine returned to basal levels 10 min after orgasm. Cortisol levels remained unaltered in the experimental condition until orgasm was reached and slightly declined thereafter. In contrast, participants in the control condition showed a continuous decline in cortisol levels throughout the session ($F_{(10,90)} = 3\cdot13$, $P<0.01$; Fig. 2).

Pituitary and gonadal hormones The most significant impact of sexual activity on plasma pituitary hormones was observed for prolactin. Basal prolactin levels (interval 1) did not differ in the experimental session compared with the control session. Furthermore, there was only a small and non-significant increase in prolactin concentrations during both sexual arousal and masturbation (interval 2 to 7). However, during and immediately after orgasm prolactin concentrations significantly increased, and remained highly elevated for the remainder of the session ($F_{(10,90)} = 16\cdot70$, $P<0.001$; Fig. 3).

Plasma concentrations of oxytocin did not differ during baseline, sexual arousal and masturbation compared with the control condition. Orgasm produced an increase in oxytocin plasma levels (interval 9 and 10), which returned to basal values 10 min after orgasm (interval 11). However, due to a large interindividual variance these alterations did not reach statistical significance ($F_{(10,80)} = 1\cdot83$, $P=0.068$; Fig. 3).

Sexual arousal and orgasm did not alter plasma concentrations of LH, FSH, vasopressin and testosterone (only the vasopressin data shown; Fig. 3).

Discussion

In the current study, plasma samples were continuously analyzed at 2-min intervals to investigate the effects of

Figure 3 Plasma concentrations of prolactin, oxytocin, and vasopressin, analyzed at 2-min intervals for the experimental (■) and control (□) condition. Sample 1 represents the basal value. Samples 2 to 10 were drawn during sexual arousal and masturbation, with sample 8 representing the orgasm and samples 9 and 10 the postorgasmic phase. Sample 11 was drawn 10 min after orgasm and displayed the recovery phase. Data are presented as means ± S.E.

sexual arousal and orgasm on plasma concentrations of catecholamines, cortisol, prolactin, LH, FSH, testosterone, vasopressin and oxytocin before, during and after masturbation-induced orgasm in males. The study revealed two major findings. First, orgasm induced an immediate, pronounced, and long-lasting increase in plasma prolactin levels, while sexual arousal alone did not affect this hormone. Secondly, although plasma oxytocin levels peaked after orgasm with a rapid decline to baseline levels, this effect was clearly of less consistency when compared with the prolactin response. In addition, the current study confirmed that sexual arousal induces transient sympathoadrenal activation, while not altering plasma levels of LH, FSH, testosterone, and vasopressin.

Although few studies have examined the effects of sexual arousal and orgasm on the plasma concentrations of oxytocin and vasopressin in humans, these hormones have been considered important in the regulation of acute sexual arousal. Vasopressin has been shown to increase during sexual arousal but not orgasm (Murphy et al. 1990), whereas oxytocin remained unchanged during sexual arousal. Nevertheless, oxytocin has been reported to increase during orgasm in men and women, although the increase has varied between 20 and 360%. Moreover, no control groups were included in these studies (Carmichael et al. 1987, Murphy et al. 1987, 1990, Carmichael et al. 1994, Blaicher et al. 1999). The current study demonstrated an increase in plasma oxytocin concentrations immediately after orgasm, followed by a rapid decline to baseline levels within 10 min. However, these effects were less consistent. In contrast, we demonstrated that prolactin might be the most prominent and easily detectable endocrine marker of orgasm in men. Although slight elevations of prolactin were observed during sexual arousal and masturbation, pronounced significant increases were only detected immediately after orgasm (Exton et al. 2000, Krüger et al. 2002).

However, the differences in the time courses of catecholaminergic, oxytocinergic and prolactinergic responses demonstrated by this study are probably not only due to differences in the duration of secretory bursts but also depend on different plasma half-lives of catecholamines (10–20 s), oxytocin (5–12 min) and prolactin (26–37 min) (Molitch et al. 1987, Nunley et al. 1991, Graves 1995). However, the further increase in prolactin levels in the two samples drawn immediately after orgasm indicates that this response probably also depends on a more sustained pituitary secretion.

Supporting our hypothesis, this study demonstrates that the pronounced prolactin release induced by orgasm can be ascribed to the immediate postorgasmic phase (Exton et al. 1999, 2000, 2001, Krüger et al. 2002). Sexual arousal and stimulation per se does not alter prolactin levels significantly (Exton et al. 2000). Postorgasmic changes in plasma prolactin levels might be of crucial interest for the interpretation of refractoriness and loss of sexual drive.

There is clinical and experimental evidence that the prolactin response to orgasm may not only affect reproductive organs (Outhit et al. 1993, Bole-Feysot et al. 1998, Goffin et al. 1999), but also may play an important role in the control of acute sexual drive after orgasm. This position is supported by a wealth of data from both animal and human studies demonstrating a marked inhibitory effect of hyperprolactinemia on sexual drive, arousal and gonadal function (Doherty et al. 1986, 1990, Walsh & Pullan 1997, Yazigi et al. 1997, Rehmann et al. 2000). Importantly, these effects are reversed upon pharmacological or surgical restoration of normal prolactin levels (De Rosa et al. 1998, Verhelst et al. 1999).

It has recently been hypothesized that prolactin may represent a negative feedback mechanism whereby this hormone may modify the activity of dopaminergic neurons in the CNS that are regarded as controlling different aspects of sexual behavior (Haake et al. 2002, Krüger et al. 2002). Although prolactin is not able to pass the blood–brain barrier due to its size (199 amino acid peptide), it may reach dopaminergic areas via the blood–cerebrospinal fluid barrier and the circumventricular organs (Sobrinho 1993, Gangong 2000). Besides a short-loop feedback to tuberoinfundibular dopaminergic neurons regulating its own release (DeMaria et al. 1999), peripheral prolactin may be able to affect dopaminergic neurons in the nigrostriatal and mesolimbocortical system and the medial preoptic area. Animal studies have demonstrated that these sites have a high density of prolactin receptors and that they are responsible for the regulation of genital responses, appetitive behavior and motor activity (Hull et al. 1999, Krüger et al. 2002).

Thus, these data corroborate the hypothesis that the orgasm-induced prolactin increase represents an endocrine feedback mechanism to CNS centers controlling acute sexual drive and behavior. This complements data from a recent single case study, which showed that a multiorgasmic male demonstrated a striking absence of orgasm-induced prolactin secretion that paralleled an extremely short refractory period (Haake et al. 2002).

In summary, this study demonstrates transient sympathoadrenal activation during sexual activity, reflected by increases in epinephrine and norepinephrine plasma levels together with increased cardiovascular activity. While vasopressin, LH, FSH, and testosterone remained unaltered by sexual arousal and orgasm, oxytocin and prolactin levels peaked immediately after orgasm. However, only plasma prolactin levels increased significantly after orgasm indicating that prolactin may represent a prominent, sustained and reliable endocrine marker of orgasm. Although different plasma half-lives have to be considered, the longer lasting response of postorgasmic prolactin elevation supports the hypothesized biological impact of this hormone, whereas short alterations of oxytocin concentrations during orgasm may simply reflect contractile properties on reproductive tissue like the uterus

(Evans 1997, Meston & Frohlich 2000). Finally, prolactin is an easily detectable and economical endocrine parameter for investigations in sexual sciences.

Acknowledgement

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