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Effects of Sexual Arousal on Lymphocyte Subset Circulation and Cytokine Production in Man

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Key Words
Sexual activity · Lymphocytes · Prolactin · Catecholamine · Cortisol · Natural killer cells

Abstract
Objective: Sexual arousal and orgasm induce an increase in sympathetic activity as well as in catecholamine and prolactin plasma concentrations. However, the effects of sexual arousal and orgasm on immune functions in man are unknown. Thus, this study investigated the effects of masturbation-induced orgasm on lymphocyte circulation and cytokine production in healthy young males. ***Methods:*** In a crossover design, 11 volunteers completed an experimental condition in which they were asked to masturbate until orgasm and to participate in a control condition without sexual activity. Blood was drawn continuously for determination of endocrine parameters. In addition, leukocyte and lymphocyte subsets were analyzed via flow cytometry, and the production of lipopolysaccharide-induced interleukin 6 and tumor necrosis factor alpha was measured before and then 5 and 45 min after the orgasm. ***Results:*** The results confirmed transient increases in adrenaline and prolactin plasma concentrations. Sexual arousal and orgasm increased the absolute number of leukocytes, in particular natural killer cells (CD3–CD16+CD56+), in the peripheral blood. In contrast, T cell (CD3+) and B cell (CD3–CD20+) subpopulations as well as the production of interleukin 6 and tumor necrosins factor alpha remained unaffected by sexual activity. ***Conclusion:*** These findings demonstrate that components of the innate immune system are activated by sexual arousal and orgasm.

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Introduction

It is well established that sexual arousal and orgasm affect cardiovascular and neuroendocrine parameters in man [1]. We have recently demonstrated in a series of studies that sexual stimulation increases cardiovascular activity and catecholamine plasma levels. Furthermore, orgasm induced a pronounced and long-lasting increase in the prolactin plasma concentration [1–7].

From an evolutionary viewpoint, sexually transmitted diseases present a threat to survival and sexual reproduc-

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tion [8, 9]. However, only a few animal studies have so far investigated the effects of sexual behavior on immune system functions. In male hamsters, splenic natural killer (NK) cell activity and primary antibody response were found to be suppressed shortly after mating [10, 11]. In contrast, it was demonstrated that the number of brain mast cells significantly increased in male mice after mating [12], and promiscuous behavior was shown to increase blood leukocyte numbers in primates [13]. Moreover, little is known regarding the effects of acute sexual activity on immune system functions in animals [14], and data about the regulation of immune system functions by sexual stimulation in humans are completely lacking.

Thus, in order to investigate whether and to what extent sexual arousal and orgasm induce changes in cellular immune functions in man, the present study analyzed the effects of masturbation-induced orgasm on cardiovascular and neuroendocrine parameters, lymphocyte subset circulation, and lipopolysaccharide (LPS) induced interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) production.

Subjects and Methods

Subjects

Eleven volunteers were recruited via an advertisement at the University Clinic of Essen. All participants underwent an intensive semistructured clinical interview, and subjects with confounding physical or mental health problems were excluded. Volunteers with drug or alcohol abuse, medication intake, or sexual dysfunctions were also excluded from participation. All subjects reported to be exclusively heterosexual and to have a relaxed attitude towards masturbation. The mean age of the participants was 37 ± (SE) 2.7 years. The volunteers were paid for participation in the study. All experimental procedures were approved by the Ethics Committee for investigation using human subjects of the University Clinic of Essen.

Experimental Paradigm

The volunteers were requested to refrain from any kind of sexual activity and to avoid alcoholic beverages or other drugs 24 h prior to the laboratory investigation. A balanced crossover design was implemented, involving two sessions on consecutive days, with each session commencing at 14:00 h [1]. The subjects sat in a comfortable chair in front of a video screen. The experimental condition was composed of three video sequences, each lasting 20 min. The first and last sections were composed of a documentary film. The middle 20 min of the experimental video were composed of an erotic film. Following 10 min viewing of the erotic video, the subjects in the experimental condition were required to masturbate until orgasm. In the control condition, the participants viewed a neutral documentary video for 60 min and did not masturbate.

Blood Collection and Hormone Analysis

To ensure accuracy of measurements and privacy of the participants, an intravenous cannula was inserted into a brachial vein and then connected to a heparinized silicone tubing that passed through the test room wall into the adjoining room. The use of a minipump allowed adjustment of blood flow to 2 ml/min. Blood was collected into EDTA tubes which were changed every 10 min, so that the temporal development of endocrine measures could be followed. Additionally, blood samples for immunological assessment were separated 5 min after video start and 5 and 45 min after the orgasm (35 min and 75 min after video start, respectively). Samples for endocrine analyses were centrifuged at 4 °C and plasma stored at –70 °C until assayed. The prolactin levels were determined by commercial assays on an automated chemiluminescence immunoassay system (ACS 180; Bayer Diagnostics, Ludwigshafen, Germany). All samples were analyzed in duplicate. The intra- and interassay coefficients of variance for prolactin were 2.5 and 3.6%, respectively. The catecholamine plasma levels were measured by high-pressure liquid chromatography. The inter- and intra-assay variabilities for noradrenaline were 8.0 and 6.2%, respectively, and for adrenaline 5.1 and 4.0%, respectively.

Cardiovascular Monitoring

In parallel to continuous blood sampling, heart rate and systolic and diastolic blood pressures were measured continuously via a finger cuff connected to a blood pressure monitor (Finapres; Ohmeda, Louisville, Colo., USA). The cables of the finger cuff passed through the wall to the adjoining room connecting to a computer. Cardiovascular parameters were sampled every 30 s. For statistical analysis, mean heart rate and blood pressure were calculated for each 10-min time interval, corresponding to the blood samples analyzed during this 10-min interval.

Leukocyte Subsets

The collected whole blood was preserved with EDTA and maintained at room temperature. WBC counts were performed to quantify absolute leukocyte numbers as well as lymphocyte, monocyte, and granulocyte populations (Beckman Coulter Electronics, Krefeld, Germany). Flow cytometry (FACSCalibur; Becton Dickinson, San Jose, Calif., USA) using CellQuest software was used to analyze lymphocyte subsets. Positive two- and three-color staining was used with monoclonal antibodies conjugated to either fluorescein isothiocyanate , phycoerythrin, or peridinin-chlorophyll-protein (Becton Dickinson and Dako, Hamburg, Germany). The fluorescence compensation was performed using CaliBRITE beads and FACSComp software (Becton Dickinson). Optimal amounts of antibodies were used, and 10,000 events were analyzed per tube. Appropriate isotypic controls were used for each assay to determine nonspecific staining. Absolute numbers of lymphocyte subsets were calculated from the WBC differential and from the percentages of gated lymphocytes analyzed by flow cytometry.

Cytokine Analysis

Whole blood was collected in tubes with sodium heparin and incubated with LPS (100 ng/ml for 4.5 h at 37 °C, 5% CO_2). The samples were centrifuged at 1,400 rpm for 15 min at 4 °C. The supernatants were collected and stored at –80 °C. The cytokines were analyzed by commercially available enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, Minn., USA). Each sample was quantified in duplicate and measured at 450 nm. The intra-assay

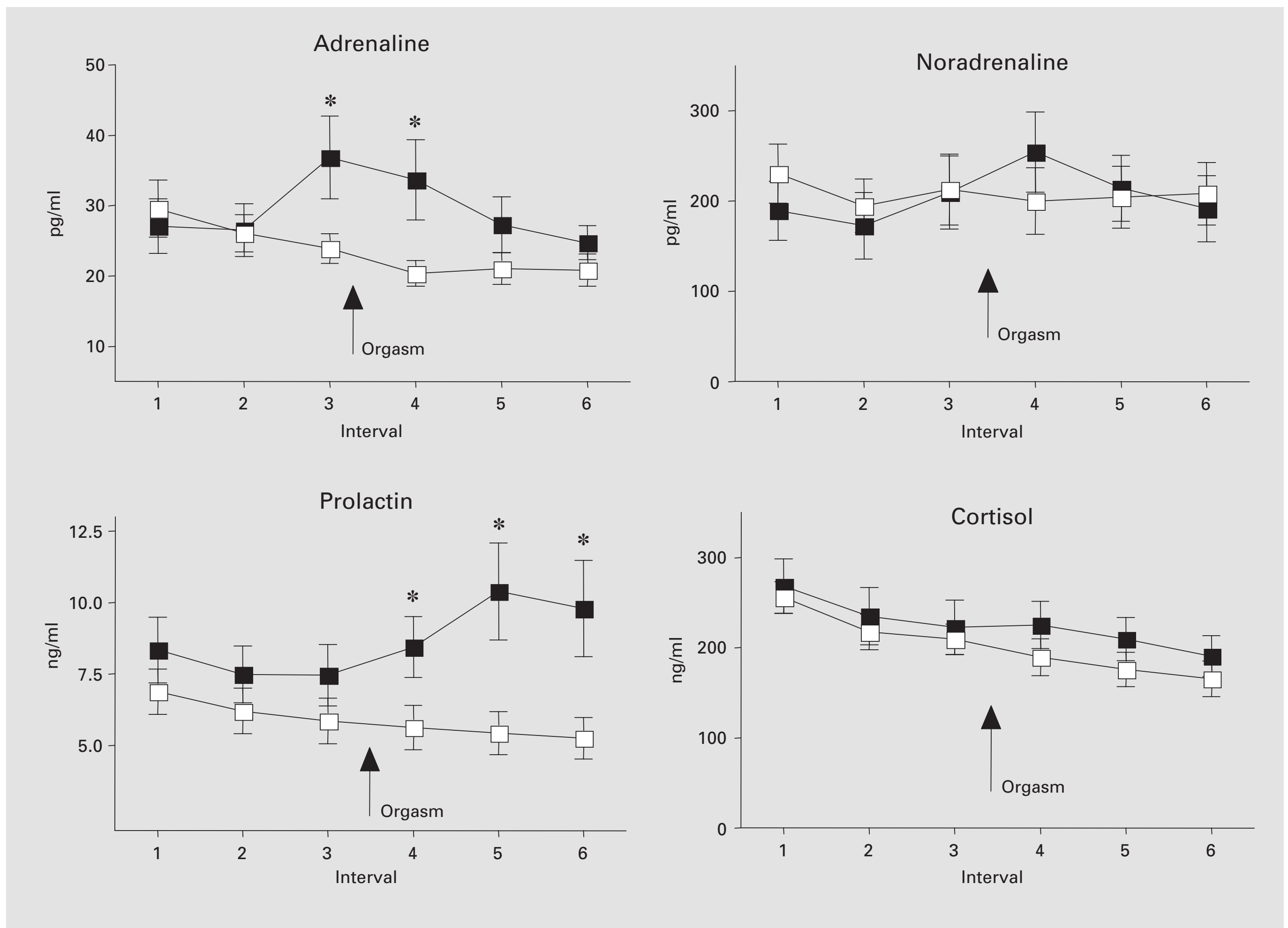

Fig. 1. Mean (± SEM) plasma concentrations of adrenaline, noradrenaline, prolactin, and cortisol during experimental (■) and control (□) conditions. * $p < 0.05$ as compared with the control condition (post hoc analyses).

coefficient of variation for the TNF-α assay was 4.4% and for the IL-6 assay 2.5%. The interassay coefficient of variation for the TNF-α assay was 8.7% and for the IL-6 assay 3.0%.

Statistics

Data were analyzed using two-factor ANOVA (condition × time). Unless stated otherwise, we report the condition × time interaction effect. Post hoc differences between time points were examined using Tukey's test for multiple comparisons. An α of 0.05 was considered statistically reliable for all analyses. In addition, a between-group ANOVA (order to film presentation) revealed no differences in the cardiovascular, endocrine, or immunological parameters between participants first exposed to the control session and participants who first experienced the experimental session. Thus, an order effect due to the experimental design can be excluded.

Results

As in previous studies employing an identical experimental design, the current data revealed increases in heart rate ($F = 8.05$; $p < 0.001$), diastolic blood pressure ($F = 8.03$; $p < 0.001$), and systolic blood pressure ($F = 11.12$; $p < 0.001$) together (data not shown). In parallel, we observed significantly elevated noradrenaline ($F = 8.5$; $p < 0.001$) and adrenaline ($F = 6.04$; $p < 0.001$) concentrations during sexual arousal and orgasm as compared with the control condition (fig. 1). In addition, the prolactin plasma levels peaked during orgasm and remained significantly elevated as compared with the control condition ($F = 6.45$; $p < 0.001$). In contrast, the cortisol concentrations remained unaffected (fig. 1).

Table 1. Whole WBC count (cells/µl) during experimental and control conditions (mean ± SE)

Parameter	Condition	Before	After 5 min	After 45 min
Leukocytes	Experimental	7,845 ± 484	8,818 ± 630**	8,536 ± 418*
	Control	6,682 ± 406	6,354 ± 449	7,145 ± 360
Lymphocytes	Experimental	2,081 ± 153	2,409 ± 193**	2,111 ± 178
	Control	2,271 ± 219	2,115 ± 159	2,308 ± 258

Post hoc analyses before vs. after 5 or 45 min: * $p < 0.05$; ** $p < 0.01$.

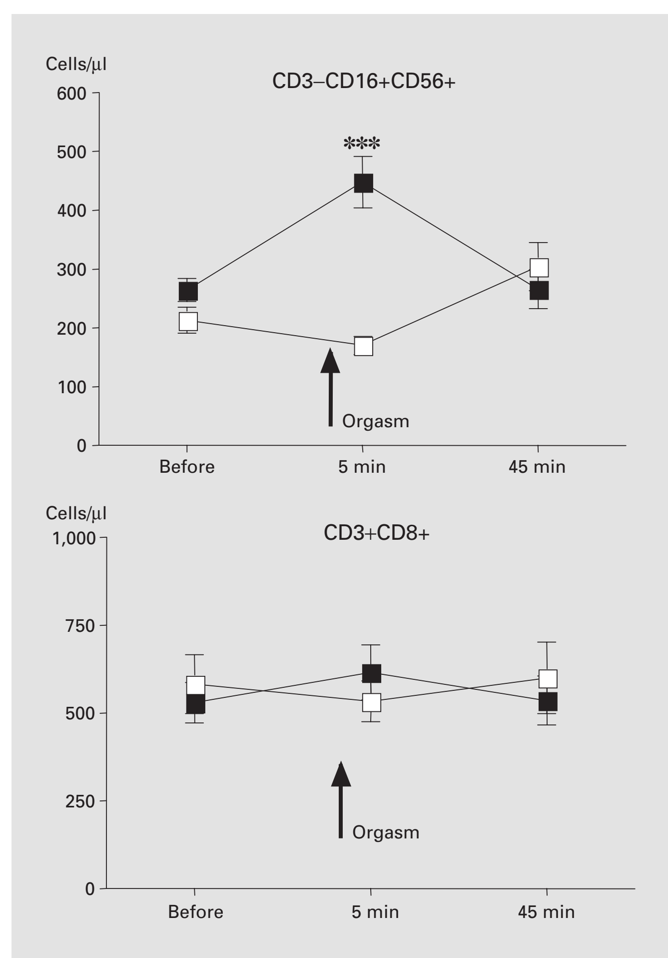

Fig. 2. Mean (± SEM) absolute numbers of NK cells (CD3–CD16+CD56+ lymphocytes) and cytotoxic/suppressor T cells (CD3+CD8+ lymphocytes) during experimental (■) and control (□) conditions. *** $p < 0.001$ as compared with 5 or 45 min after (post hoc analyses).

We observed a significant transient increase in leukocyte ($F = 5.1$; $p < 0.05$) and lymphocyte ($F = 7.0$; $p < 0.01$) numbers 5 min after the orgasm (table 1). In contrast, granulocyte and monocyte numbers did not significantly differ between the conditions (data not shown). The lymphocyte subpopulations analyzed by flow cytometry showed an increase in NK cell (CD3–CD16+CD56+) numbers ($F = 26.72$; $p < 0.001$) immediately after the orgasm which returned to baseline values 45 min after the orgasm. In parallel, the orgasm induced a moderate but statistically significant transient elevation of the cytotoxic/suppressor T cell (CD3+CD8+) numbers ($F = 4.92$; $p < 0.05$; fig. 2). In contrast, the absolute numbers of T cells (CD3+), T helper cells (CD3+CD4+), and B cells (CD3–CD20+) were not affected by sexual stimulation (data not shown).

Since proinflammatory cytokines can be increased by acute stress, we analyzed in vitro the LPS-induced production of IL-6 and TNF-α before and after the orgasm. However, the levels of both cytokines remained unaltered by masturbation-induced orgasm (data not shown).

Discussion

It has been demonstrated that an orgasm increases plasma prolactin and catecholamine concentrations in men and women [1]. Since adrenergic mechanisms have been shown to significantly affect cellular and humoral immune functions [15], this study investigated the effects of acute sexual activity on lymphocyte subset distribution and LPS-induced IL-6 and TNF-α production in healthy men. As previously demonstrated, sexual stimulation and masturbation-induced orgasm were accompanied by a pronounced elevation of prolactin and increased cardiovascular parameters and catecholamine concentrations. The present study demonstrates for the first time that acute sexual stimulation transiently increases NK-cell numbers (CD3–CD16+CD56+) and, to a much lesser

extent, CD3+CD8+ T lymphocytes in the peripheral blood. In contrast, the levels of LPS-induced proinflammatory cytokines (IL-6, TNF-α) remained unaffected by masturbation-induced orgasm.

To date, the effects of sexual activity on immune system functions have only been investigated in a few studies in different species and with contradictory results. For example, male hamsters had a decreased antibody response following copulatory activity [11] and a suppression of the NK cell activity [10]. In insects, a decreased antibacterial immune response following increased sexual activity was observed [14]. In contrast to these inhibitory effects of sexual stimulation on immune functions, promiscuous behavior in primates has been shown to increase the absolute numbers of blood leukocytes, suggesting a promiscuity-induced stimulation of immune functions [13]. Furthermore, a study in male mice demonstrated significantly increased brain mast cell numbers after mating [12]. Due to the heterogeneity of methodological approaches across species in these studies, a general interpretation of how and to what extent sexual activity is affecting immune system functions is not possible. The present study demonstrates that acute sexual stimulation and orgasm increase NK cell and, to a lesser extent, cytotoxic/suppressor T cell numbers.

The neuroendocrine response to sexual stimulation and orgasm is similar, although not identical, to the pattern observed after acute psychological stress [16]. In contrast to acute psychological stress, sexual stimulation does not induce changes in the hypothalamo-pituitary-adrenal axis, since the ACTH and cortisol plasma levels remain unchanged after orgasm [6]. However, both acute psychological stress and sexual arousal and orgasm increase the plasma concentrations of adrenaline and noradrenaline as well as the plasma levels of prolactin [17–20]. In addition, prolactin is found to be a selective neuroendocrine marker for orgasm in men and women [2–4, 6]. Since it has been demonstrated in a number of human studies that the increases in NK cells (CD3–CD16+CD56+) and cytotoxic/suppressor T lymphocytes (CD3+CD8+) after acute psychological stress are mainly mediated by catecholamines and β-adrenergic mechanisms, it might be hypothesized that the changes in lymphocyte distribution during orgasm are due to the increased sympathetic activation [15, 16, 21–25]. Further studies will be needed to focus on the mechanisms of the orgasm-induced changes in lymphocyte circulation and to analyze whether adrenergic mechanims or other neuroendocrine factors, in particular the increased levels of prolactin, are responsible for the observed effects [26–29].

Previous studies have shown increased levels of IL-6 and TNF-α after psychological stress [30, 31]. Therefore, we analyzed the LPS-induced production of IL-6 and TNF-α levels before and after sexual arousal and orgasm. However, in this study, we observed no differences between the experimental and control conditions in IL-6 or TNF-α levels within 45 min after the orgasm. Despite the fact that sexual activity does not affect these proinflammatory cytokines, it is possible that changes in cytokine production are delayed after sexual stimulation and orgasm. Along these lines it has recently been demonstrated that an increase in IL-6 production occurred 2 h after the induction of various behavioral tasks [32].

In summary, this study demonstrates for the first time that sexual activity and orgasm induce transient increases in the circulation of lymphocyte subpopulations, in particular NK cell numbers, in man. Analogous to a fight/flight response, these findings may represent a reproductive reflex which activates components of the innate immune system during sexual arousal and orgasm. The effects of orgasm on peripheral lymphocyte subsets were restricted to NK cells and had minor or no effects on T or B cell subsets and showed no effects on cytokine production, indicating limited and selective effects of orgasm on immune system functions in parallel with its selective and short-lived neuroendocrine effects.

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