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G. Vila, M. Riedl, M. Resl, A. J. van der Lely, L. J. Hofland, M. Clodi and A. Luger

J. Endocrinol., October 1, 2009; 203 (1): 175-179.

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Oxytocin attenuates NADPH-dependent superoxide activity and IL-6 secretion in macrophages and vascular cells

A. Szeto, D. A. Nation, A. J. Mendez, J. Dominguez-Bendala, L. G. Brooks, N. Schneiderman and P. M. McCabe

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Oxytocin alleviates the neuroendocrine and cytokine response to bacterial endotoxin in healthy men

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Clodi M, Vila G, Geyeregger R, Riedl M, Stulnig TM, Struck J, Luger TA, Luger A. Oxytocin alleviates the neuroendocrine and cytokine response to bacterial endotoxin in healthy men. *Am J Physiol Endocrinol Metab* 295: E686–E691, 2008. First published July 1, 2008; doi:10.1152/ajpendo.90263.2008.—Oxytocin is a hormone and neurotransmitter found to have anti-inflammatory functions in rodents. Here we used experimental bacterial endotoxemia to examine the role of exogenous oxytocin administration on innate immune responses in humans. Ten healthy men received, in a randomized, placebo-controlled, crossover design, placebo, oxytocin, LPS, and LPS + oxytocin. Oxytocin treatment resulted in a transient or prolonged reduction of endotoxin-induced increases in plasma ACTH, cortisol, procalcitonin, TNF- α , IL-1 receptor antagonist, IL-4, IL-6, macrophage inflammatory protein-1 α , macrophage inflammatory protein-1 β , monocyte chemoattractant protein-1 (MCP-1), interferon-inducible protein 10, and VEGF. In vitro, oxytocin had no impact on LPS effects in releasing TNF- α , IL-6, and MCP-1 in monocytes and peripheral blood mononuclear cells from healthy human donors. In summary, oxytocin decreases the neuroendocrine and cytokine activation caused by bacterial endotoxin in men, possibly due to the pharmacological modulation of the cholinergic anti-inflammatory pathway. Oxytocin might be a candidate for the therapy of inflammatory diseases and conditions associated with high cytokine and VEGF levels.

neuroendocrinology; hypothalamic-pituitary-adrenal; cytokines

SYSTEMIC INFLAMMATION IS IMPLICATED in the pathophysiology of many diseases, including chronic inflammatory diseases, infections, sepsis, atherosclerosis, and obesity (11, 13, 22, 25). The most widely used model for testing the systemic host response to infection and inflammation in humans is the intravenous administration of bacterial endotoxin, which contains LPS parts of the *Escherichia coli* bacterial wall (8). Human response mechanisms to this challenge are integrated via coordinated neuroendocrine-immune interactions (5, 9, 30).

Physiological conditions associated with a reduced hypothalamic-pituitary-adrenal (HPA) response to different stressors include the peripartal period and lactation (12, 26). Common denominators of these conditions are high intrahypothalamic and plasma oxytocin concentrations. Oxytocin is a highly conserved nonapeptide with hormone and neurotransmitter properties that is synthesized in the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus (10). It exerts

direct excitatory effects on vagal neurons and has classic reproduction-related functions (1, 14, 20).

A large body of evidence suggests a regulatory role of oxytocin during immune and inflammatory responses in animal models. Oxytocin displays anti-inflammatory effects, abolishes the sepsis-induced increase in TNF- α , and protects against multiple organ damage (6, 7, 16, 24). In contrast, oxytocin-deficient mice exhibit increased stress responses associated with a significant hyperactivation of the HPA axis (2).

Here we present a randomized, placebo-controlled, crossover trial, conducted to test the effect of continuous intravenous oxytocin infusion on LPS-induced systemic inflammation in 10 healthy men. In addition, we investigated whether oxytocin directly affects the LPS-induced cytokine release from peripheral blood mononuclear cells (PBMCs) of healthy human donors in vitro.

METHODS

Study participants. Ten healthy men, aged 20–40 yr, were included in the study after giving informed consent. The trial was approved by the Institutional Review Board. All participants were free of medication, found to be healthy upon clinical examination, and had normal liver, renal, and endocrine functions.

Clinical procedures. Each subject was studied on four different occasions with intervals of at least 3 wk. Following a randomized, placebo-controlled, crossover design, we administered intravenously: 1) placebo (isotonic saline); 2) oxytocin (1 pmol·kg⁻¹·min⁻¹ given in isotonic saline for 90 min); 3) a bolus of LPS (20 IU/kg body wt, corresponding to 2 ng/kg; National Reference *Escherichia coli* Endotoxin, USP Convention, Rockville, MD); and 4) 20 IU/kg LPS + 1 pmol·kg⁻¹·min⁻¹ oxytocin for 90 min. The study lasted 6 h. The subjects received an infusion of isotonic saline, which started at 500 ml/h at time point -30 min, was reduced to 200 ml/h at 0 min and maintained at 100 ml/h from the 90th minute till the 6th hour. Heart rate and ECG were monitored online (Lohmeier M607, Siemens, Munich, Germany), and blood pressure was measured every 30 min. Body temperature was determined orally. Blood samples were drawn every 30 min for the first 2 h and every 60 min afterwards in EDTA containing tubes. All subjects were discharged in good health ~7–8 h after LPS administration.

Hormone and cytokine measurements. Blood samples were immediately cooled and centrifuged for 10 min at 3,000 rpm, 4°C, and plasma aliquots were immediately frozen at -20 °C. Plasma oxytocin and ACTH were measured using commercial RIA kits (Peninsula Laboratories, San Carlos, CA). Procalcitonin (PCT) was measured using the BRAHMS Procalcitonin Sensitive LIA kit (BRAHMS AG,

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Hennigsdorf, Germany) (21). The plasma levels of TNF- α , IL-1 receptor antagonist (IL-1ra), IL-4, IL-6, interferon-inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 α (MIP-1 α), macrophage inflammatory protein-1 β (MIP-1 β), and VEGF were measured using the Fluorokine MultiAnalyte Profiling Base Kit A (R&D, Minneapolis, MN). All samples taken over the 4 study days for each individual subject were analyzed at the same time and in duplicates.

TNF- α , IL-6, and MCP-1 released by CD14⁺ monocytes were measured in cell-free supernatants by quantitative sandwich enzyme immunoassay kits, according to the manufacturer's instructions (all R&D Systems, Minneapolis, MN).

Cell isolation and culture. PBMCs were isolated from acid citrate dextrose buffy coats of healthy donors. CD14⁺ monocytes were obtained by magnetic cell sorting using anti-CD14-conjugated magnetic microbeads (Miltenyi Biotec, Bergisch Gladbach, Germany). CD14⁺ monocytes (2×10^6) or PBMCs (10^6 cells/ml) were cultured in human serum albumin-containing X-Vivo 10 medium (Cambrex Bio Science, Verviers, Belgium) in 12-well plates [stimulated with 100 ng/ml LPS (*Escherichia coli* 0111:B4), Sigma, St. Louis, MO] for 2, 4, and 24 h. Different concentrations of oxytocin (Sigma) or vehicle control (0.1% water) were added to the cells 30 min before adding LPS.

Statistical analysis. Temperature, hormone, cytokine, chemokine, and PCT data are expressed as means \pm SE. Temperature, cortisol, ACTH, and PCT values obtained during the 4 study days were analyzed by repeated-measures ANOVA. The interaction between time and treatment was considered the term of interest. When this test was positive, post hoc statistics were performed by means of Bonferroni-corrected paired *t*-tests, and these values are given in the RESULTS section. Areas under the curve (AUCs) for the cytokine responses to the intervention were calculated by trapezoidal integration. AUC data are expressed as means \pm SD and compared between groups by one-way ANOVA, followed by post hoc statistics. Data from in vitro experiments were analyzed by ANOVA in combination with Scheffé's test. A *P* value < 0.05 was considered significant.

RESULTS

Febrile and hormone response. LPS administration induced a significant increase in body temperature (LPS vs. placebo, $P < 0.001$), which was significantly altered by infusion of oxytocin only toward the end of the observation period ($P = 0.038$, $P = 0.025$, and $P = 0.029$ between LPS + oxytocin and LPS treatments at time points 330, 345, and 360 min, respectively) (Fig. 1). Administration of oxytocin elevated within 10

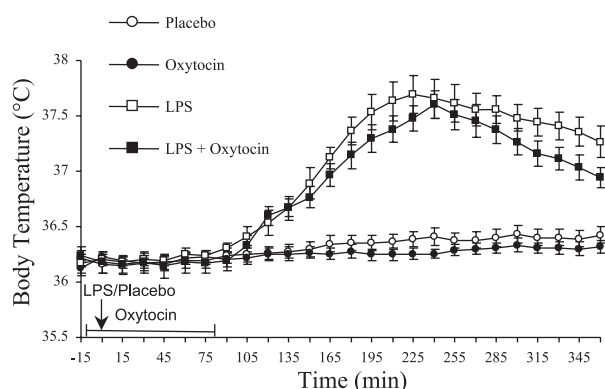


Fig. 1. Body temperature changes on the 4 study days. LPS (2 ng/kg iv, time $t = 0$ h) increased body temperature. Oxytocin (continuous infusion of 1 pmol \cdot kg⁻¹ \cdot min⁻¹ between $t = -10$ and 80 min) induced significant changes in the LPS-induced increase in temperature in the last 30 min of the study. Values are means \pm SE.

min plasma oxytocin levels ($P = 0.021$), which reached peak values at time point 60 min ($P < 0.001$) (Fig. 2A). Circulating oxytocin then began to decline 10 min after the infusion was stopped, but remained significantly elevated until time point 120 min ($P < 0.001$) (Fig. 2A). Plasma concentrations of ACTH (Fig. 2B) and cortisol (Fig. 2C) remained unchanged during oxytocin treatment, but increased after the LPS bolus ($P = 0.027$ for ACTH at 120 min and $P = 0.043$ for cortisol at 90 min when comparing LPS vs. placebo). A significantly reduced increase in plasma ACTH was observed at time point 120 min: 36.1 ± 5.9 pg/ml in the LPS + oxytocin group vs. 69.6 ± 14.8 pg/ml in the LPS group ($P = 0.019$) (Fig. 2B). The LPS-induced increase in plasma cortisol was also alleviated in the LPS + oxytocin group at time points 90 min ($P = 0.03$) and 120 min ($P = 0.01$) (Fig. 2C).

Cytokines, chemokines, and VEGF. LPS significantly increased plasma levels of inflammatory cytokines (TNF- α , IL-4, and IL-6; Fig. 3, A–C) and chemokines (MCP-1, MIP-1 α , MIP-1 β , and IP-10; Fig. 3, E–H). Oxytocin infusion, although lasting only 90 min, significantly attenuated the cytokine and chemokine response to endotoxin, as measured by the respective AUCs (Table 1). Based on the fact that oxytocin infusion resulted in varying plasma oxytocin concentrations throughout the study, we calculated AUCs for three different time periods: 0–120 min (significantly elevated plasma oxytocin levels), 0–240 min (until the reduction of plasma oxytocin level to basal values), and 0–360 min (the full length of the study). AUCs (0–120 min) of TNF- α , IL-4, IL-6, IL-1ra, MCP-1, IP-10, MIP-1 α , and MIP-1 β were significantly lower on the LPS + oxytocin protocols compared with LPS alone. Moreover, the attenuation in IL-4, IL-6, and MCP-1 remained significant throughout the study, as demonstrated by significant differences between AUC (0–360 min) in LPS days vs. LPS + oxytocin days. In addition, oxytocin induced a significant decrease of the LPS-induced plasma VEGF (Fig. 3D, Table 1).

PCT. To further evaluate the impact of oxytocin on the severity of endotoxemia, we measured the plasma concentrations of PCT, a diagnostic and prognostic biomarker in sepsis (17). Oxytocin significantly reduced the LPS-induced increase in PCT, which presented significant differences at the 240th min (0.178 ± 0.05 ng/ml on LPS days compared with 0.072 ± 0.01 ng/ml on LPS + oxytocin days, $P = 0.043$), at the 300th min ($P = 0.033$), and at the 360th min ($P = 0.035$) (Fig. 4).

We took into consideration the possibility that repeated injections of endotoxin itself may result in an altered immune response, inducing resistance or tolerance in humans. Therefore, the subjects received the four treatments in a randomized order. In addition, we compared the changes in plasma ACTH, cortisol, cytokines, chemokines, VEGF, and PCT between volunteers randomized to receive LPS before the application of LPS + oxytocin ($n = 5$) and volunteers randomized to receive LPS + oxytocin before the administration of LPS ($n = 5$). Results were similar to those obtained from all volunteers being treated with LPS vs. all volunteers having received LPS + oxytocin.

In vitro study in monocytes and PBMCs. To detect a possible direct effect of oxytocin on LPS-induced cytokine release, we isolated monocytes from four healthy donors and treated them with oxytocin at concentrations of 0, 10 pM, 100 pM, 1 nM, and 10 nM for 30 min before addition of LPS for 2, 4, or 24 h.

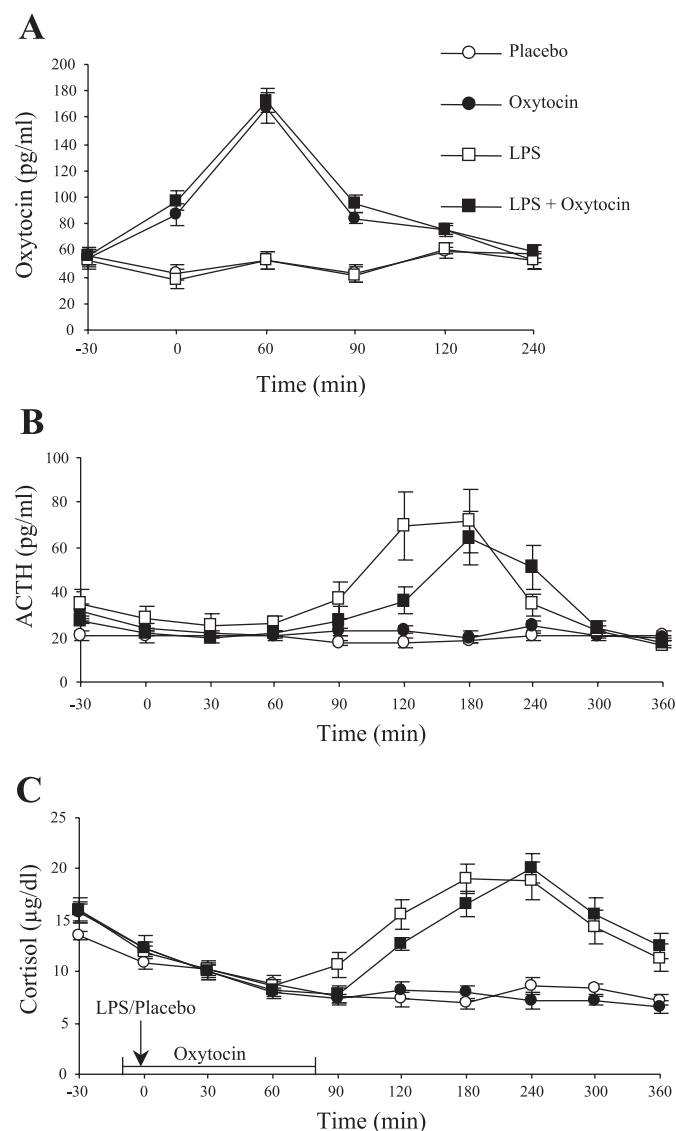


Fig. 2. Hormone levels in response to endotoxin and oxytocin. Plasma concentrations are shown of oxytocin (A), ACTH (B), and cortisol (C) in response to placebo, oxytocin ($1 \text{ pmol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during 90 min, $t = -10$ to 80 min), LPS (2 ng/kg iv, $t = 0$ h), and LPS + oxytocin. Values are means \pm SE.

TNF- α , IL-6, and MCP-1 were measured in the cell-free supernatant. Pretreatment with oxytocin did not induce any significant differences in the cytokine amounts released from unstimulated as well as LPS-stimulated monocytes (Fig. 5). Similar results were obtained with unseparated PBMCs containing monocytes and lymphocytes (data not shown).

DISCUSSION

This study is the first to investigate the role of oxytocin on the neuroendocrine and inflammatory responses to endotoxemia in humans. We have shown that oxytocin treatment results in a significant, either transient or prolonged, suppression of the release of ACTH, cortisol, TNF- α , IL-1ra, IL-4, IL-6, MIP-1 α , MIP-1 β , MCP-1, IP-10, and VEGF in healthy volunteers. Attenuation of IL-1ra and MIP-1 α occurs as long as oxytocin plasma levels are elevated (until time point 120 min) and ceases once they return to baseline. Other cytokines/

chemokines remained significantly suppressed for a longer period, whereas the response of IL-4, IL-6, and MCP-1 was dampened throughout the study. Oxytocin was found to have no effect on LPS-induced TNF- α , IL-6, and MCP-1 production from human monocytes and PBMCs in vitro.

The beneficial role of oxytocin in endotoxemia is further supported by the fact that it significantly reduces PCT. PCT is the precursor of calcitonin, which is released in response to LPS, bacterial infection, and sepsis (18). PCT is an efficient diagnostic biomarker and superior to C-reactive protein for sepsis, severe sepsis, and septic shock (29). It is also an accurate prognostic factor, as high maximum PCT levels and daily PCT increases are early independent predictors of all-cause mortality in sepsis (17).

The release of endotoxin from bacteria is generally believed to be the initial event in the development of bacterial inflammation and sepsis. LPS activates inflammatory cells of the myeloid lineage, subsequently resulting in the amplification of the acute inflammatory response via the release of various cytokines, such as TNF- α , IL-1 β , IL-6, IL-8, and nitric oxide. The body tightly regulates the inflammatory process by releasing anti-inflammatory cytokines that protect against self-destruction (22, 28). In addition, the autonomous nervous system participates in controlling cytokine release. It has been reported that direct electrical stimulation of the efferent vagus nerve attenuates cytokine release in endotoxemia, whereas vagotomy exacerbates the inflammatory response to endotoxins (27).

The HPA axis was also reported to participate in the early phase of endotoxic shock (5). In rats, LPS has been shown to significantly increase the number of cells showing Fos immunoreactivity in the PVN and SON nuclei of the hypothalamus, thereby raising plasma concentrations of vasopressin and oxytocin (19). Lesions of the anterolateral third ventricle significantly reduced LPS-induced oxytocin, vasopressin, and ACTH secretion (3). Therefore, oxytocin might be considered as part of the neuroendocrine response to bacterial endotoxin. Although several studies have shown an increase of plasma oxytocin levels in response to endotoxin in rodents, we did not find any significant changes in humans. This difference is probably due to the dosage of endotoxin used in the human studies (2 ng/kg iv) vs. the near-lethal doses (1.5 mg/kg iv) used in rodent studies. Other members of the first-phase neuroendocrine response to sepsis, namely glucocorticoids and epinephrine, inhibit cytokine synthesis and are currently used therapeutically in intensive care medicine (28). We present here for the first time that oxytocin can also alleviate the inflammatory response to endotoxemia in humans.

Oxytocin seems to slow down this acute inflammatory process, first, by reducing the secretion of TNF- α , IL-6, and IL-8. Second, oxytocin regulates the immune response by dampening anti-inflammatory cytokines, such as IL-1ra and IL-4. Our data are in agreement with previous animal studies in which sepsis-induced TNF- α excursions in Sprague-Dawley rats were abolished by oxytocin treatment (16). TNF- α excursions through acetic acid-induced colonic injury were also alleviated by oxytocin treatment (15).

The lack of direct effects of oxytocin on the LPS-induced TNF- α , IL-6, and MCP-1 secretion from human monocytes and PBMCs in vitro suggests that oxytocin does not act directly on monocytes and peripheral blood lymphocytes. Indeed, peripheral mononuclear cells do not possess the oxytocin receptor

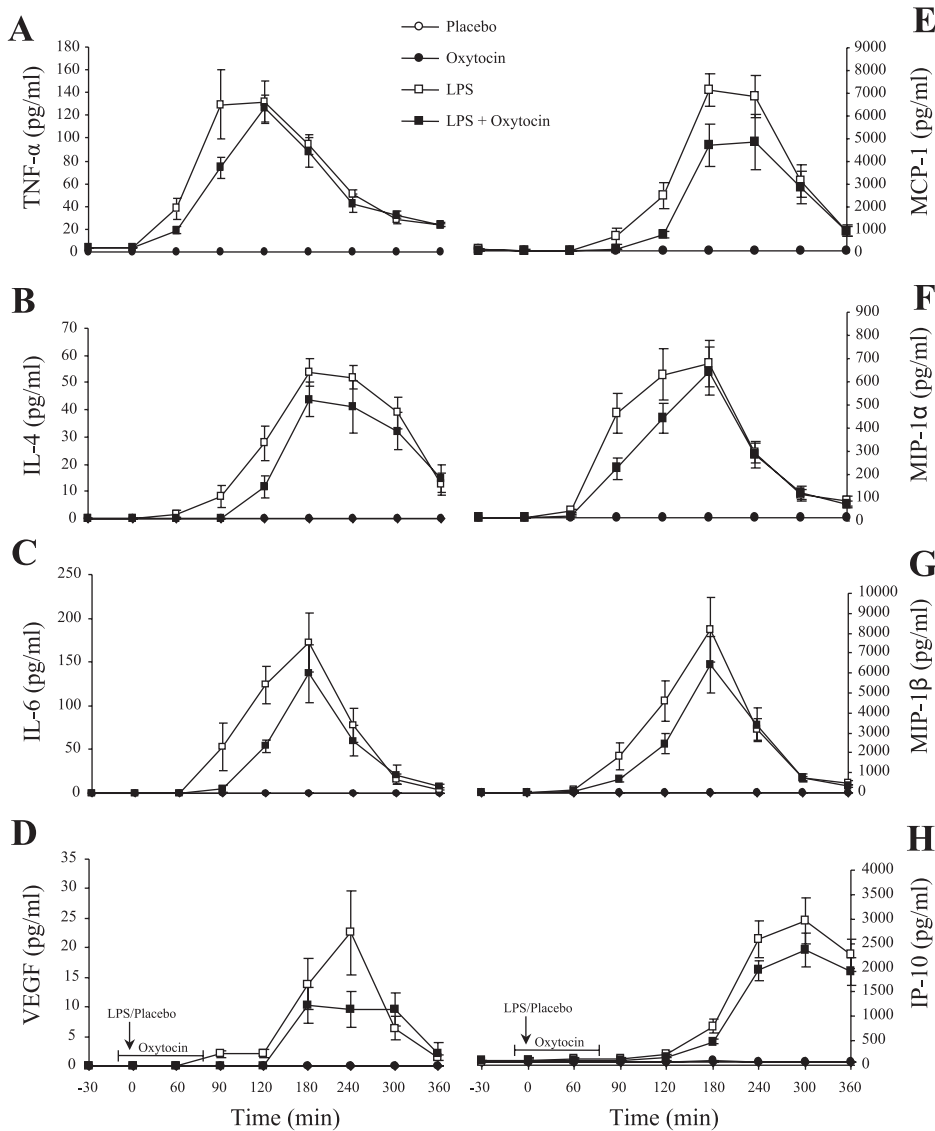


Fig. 3. Cytokine, chemokine, and VEGF responses to endotoxin and oxytocin. Plasma levels are shown of TNF- α (A), IL-4 (B), IL-6 (C), VEGF (D), monocyte chemoattractant protein (MCP)-1 (E), macrophage inflammatory protein (MIP)-1 α (F), MIP-1 β (G), and IP-10 (H) after placebo or LPS administration (2 ng/kg iv, $t = 0$ h), in the presence or absence of oxytocin infusion ($t = -10$ to 80 min). Values are means \pm SE.

(7). The contradiction between the in vivo and in vitro effects of oxytocin on LPS-induced cytokine release may be explained by the fact that oxytocin is not only a hormone, but also a neurotransmitter and neuromodulator. Hence, it might indi-

rectly modulate the release of cytokines. Considering the observation that electrical stimulation of the hypothalamic PVN nucleus influences gastric secretion and motility, McCann and Rogers (20) found that oxytocin is responsible for an

Table 1. AUC values of cytokines, chemokines, and VEGF

	AUC ₍₀₋₁₂₀₎		AUC ₍₀₋₂₄₀₎		AUC ₍₀₋₃₆₀₎	
	LPS	LPS + Oxytocin	LPS	LPS + Oxytocin	LPS	LPS + Oxytocin
TNF- α	139.3 \pm 81.2*	71.04 \pm 28.94*	311 \pm 140.6*	229.6 \pm 93.6*	377.3 \pm 153.6	296 \pm 114.7
IL-1ra	0.72 \pm 0.3*	0.44 \pm 0.2*	33.8 \pm 7.1	25.1 \pm 10.1	73.7 \pm 9.3	65.3 \pm 13.2
IL-4	10.82 \pm 10.19*	2.62 \pm 3.23*	105.7 \pm 37.6*	69.5 \pm 41.4*	176.7 \pm 62.6*	124.9 \pm 82.6*
IL-6	51.7 \pm 54.4*	17.2 \pm 9.2*	311.5 \pm 164.7*	209.3 \pm 142.9*	386.6 \pm 201.3*	264.6 \pm 205.2*
MCP-1 ($\times 10^3$)	1.13 \pm 0.97*	0.38 \pm 0.13*	13.1 \pm 5*	8.43 \pm 4.71*	22.3 \pm 5.7*	14.6 \pm 8*
MIP-1 α ($\times 10^3$)	0.43 \pm 0.22*	0.26 \pm 0.12*	1.57 \pm 0.69	1.41 \pm 0.72	1.87 \pm 0.84	1.76 \pm 0.95
MIP-1 β ($\times 10^3$)	2.16 \pm 1.68*	0.97 \pm 0.6*	14.2 \pm 0.8*	11.1 \pm 8.6*	16.8 \pm 8.5	12.6 \pm 8.2
IP-10 ($\times 10^3$)	0.25 \pm 0.24*	0.2 \pm 0.19*	2.45 \pm 0.97*	1.74 \pm 0.45*	7.82 \pm 3.26	5.9 \pm 1.8
VEGF	10.14 \pm 5.5	8.2	35.5 \pm 13.3*	25.5 \pm 10.2*	57.6 \pm 19.7*	42.9 \pm 18.2*

Values are means \pm SD. Areas under the curve at 0–120, 0–240, and 0–360 min {AUC₍₀₋₁₂₀₎, AUC₍₀₋₂₄₀₎, and AUC₍₀₋₃₆₀₎, respectively} are shown of cytokine, chemokine, and VEGF changes after placebo or LPS administration (2 ng/kg iv, time $t = 0$ h), in the presence and absence of oxytocin (1 pmol·kg⁻¹·min⁻¹ during 90 min, $t = -10$ min until $t = 80$ min). MCP-1, monocyte chemoattractant protein-1; MIP, macrophage inflammatory protein. * $P < 0.05$.

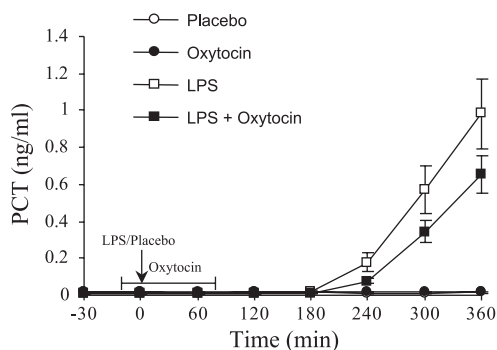


Fig. 4. Procalcitonin (PCT) levels in response to endotoxin and oxytocin. Plasma PCT concentrations are shown after placebo or LPS administration (2 ng/kg iv, $t = 0$ h), in the presence or absence of oxytocin infusion ($t = -10$ to 80 min). Values are means \pm SE.

increase in the excitability of central vagal neurons. These effects are mediated by G protein activation and a cAMP-independent pathway (1). A clinical study performed in healthy women revealed also that intravenous infusion of oxytocin is able to alter colonic motility (23). Taking together these data and the results of the present study, we hypothesize that intravenously administered oxytocin might modulate the activity of the vagal nerve and of the cholinergic anti-inflammatory pathway, thereby reducing the neuroendocrine and cytokine response to bacterial endotoxin.

Most interestingly, our data also provide evidence that oxytocin suppresses the LPS-stimulated increase in circulating VEGF. Oxytocin and its signaling pathway have been shown to inhibit growth of neoplastic cells, such as ovarian, neuroblastoma, astrocytoma, and other cell types (4). Oxytocin concentrations were shown to be increased in benign and decreased in malignant prostate disease, and changes in prostatic concentrations of oxytocin may facilitate cell proliferation (31). Oxytocin receptor is downregulated in non-small cell lung, and its ectopical expression suppresses cell growth (32). These data, as well as our finding that oxytocin inhibits the LPS-induced increase in circulating cytokines and VEGF, open new perspectives on the potential biological role of oxytocin in cancer.

Before concluding, we should discuss several limitations of this study. First, the study population included only healthy men, and we have no data on the role of oxytocin on the LPS-induced endocrine and cytokine activation in women. Second, as this is the first study coadministering LPS and oxytocin in humans, we took care to use the smallest oxytocin dose needed to achieve elevated oxytocin concentrations during the first 120 min after LPS administration. Nevertheless, the achieved maximal concentrations of 160–180 pg/ml are clearly supraphysiological. Third, LPS administration is only an experimental and self-limiting model of infection and inflammation.

In summary, this study demonstrates that pharmacological doses of oxytocin attenuate the endocrine and cytokine activa-

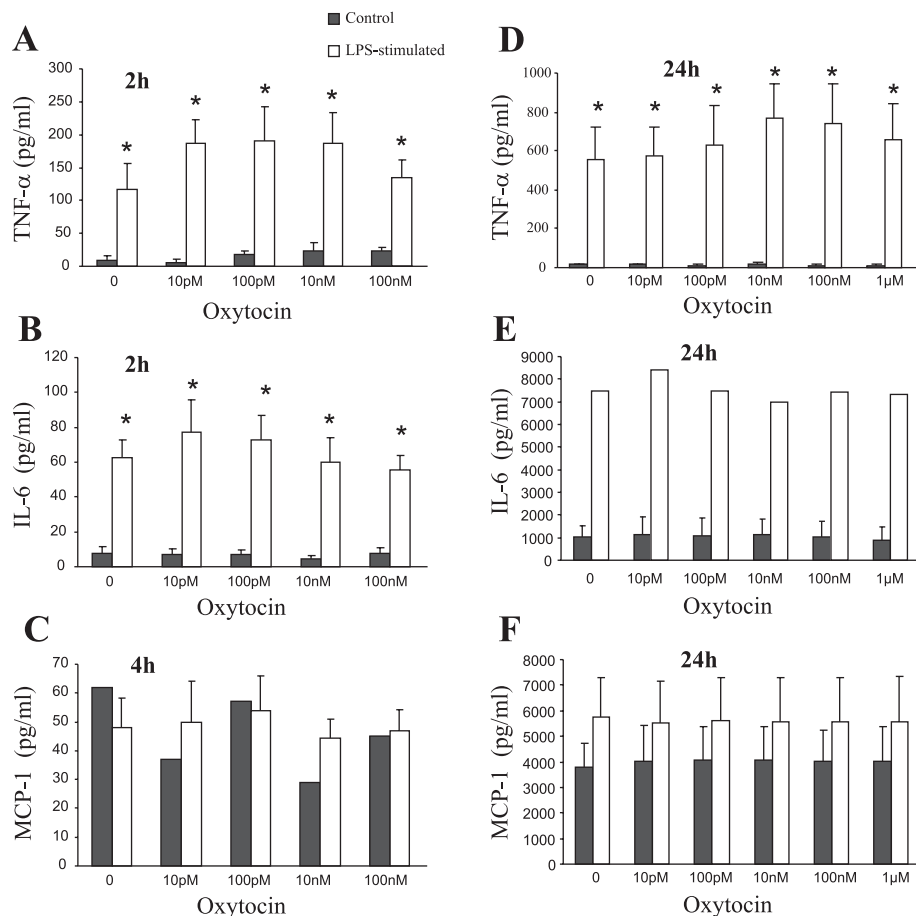


Fig. 5. TNF- α (A and D), IL-6 (B and E), and MCP-1 (C and F) secretion from human monocytes in primary culture. CD14⁺ monocytes (2×10^6) isolated from peripheral blood mononuclear cells with a purity of 95–99% were plated at 10^6 cells/ml in 12-well plates. They were treated with oxytocin at concentrations of 0, 10 pM, 100 pM, 1 nM, and 10 nM for 30 min before adding 100 ng/ml LPS for 2 (A and B), 4 (C), or 24 h (D–F). TNF- α , IL-6, and MCP-1 concentrations secreted in the supernatant were measured by ELISA. Values are means \pm SE. * $P < 0.05$.

tion following bacterial endotoxin administration in humans. Oxytocin appears to modulate innate host defense mechanisms, thereby eventually reducing an LPS-induced overshooting immune response. We currently exclude a direct effect of oxytocin on PBMCs and suggest that it might modulate the anti-inflammatory cholinergic pathway instead. Further studies are needed to establish the potential role of oxytocin in the early therapy of inflammatory diseases, sepsis, or conditions associated with high circulating cytokine and VEGF concentrations.

GRANTS

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DISCLOSURES

J. Struck is an employee of BRAHMS AG.

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