Published in final edited form as:

Int Urogynecol J. 2016 September ; 27(9): 1383–1391. doi:10.1007/s00192-016-2988-6.

Basal and stress-activated hypothalamic pituitary adrenal axis function in postmenopausal women with overactive bladder

Ariana L. Smith¹, Liisa Hantsoo^{2,4,5}, Anna P. Malykhina⁶, Daniel W. File⁷, Rita Valentino⁸, Alan J. Wein¹, Mary D. Sammel⁹, and C. Neill Epperson^{2,3,4,5}

Ariana L. Smith: Ariana.smith@uphs.upenn.edu

¹Department of Surgery, Division of Urology, Perelman School of Medicine, University of Pennsylvania, 800Walnut Street, 19th Floor, Philadelphia, PA 19107, USA

²Department of Psychiatry, University of Pennsylvania, Philadelphia, PA 19107, USA

³Department of Obstetrics and Gynecology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19107, USA

⁴Penn Center for the Study of Sex and Gender in Behavioral Health, Philadelphia, PA 19107, USA

⁵Penn Center for Women's Behavioral Wellness, Philadelphia, PA 19107, USA

⁶Department of Surgery, Division of Urology, University of Colorado School of Medicine, Aurora, CO 80045, USA

⁷Department of Mathematics & Computer Science, Muhlenberg College, Allentown, PA 18104, USA

⁸Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

⁹Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19107, USA

Abstract

Introduction and hypothesis—The aim of this study was to measure physiologic and psychologic stress reactivity in women with overactive bladder (OAB). There is growing evidence in preclinical models that central nervous system dysregulation, particularly in response to psychological stress, may contribute to lower urinary tract symptoms in women with OAB.

Methods—Postmenopausal women with OAB and healthy controls underwent Structured Clinical Interview for DSM-IV Axis I disorders (SCID) to identify those without identifiable psychiatric disease. Eligible participants underwent physiologic measures including basal (cortisol-awakening response; CAR) and stress-activated salivary cortisol levels, heart rate (HR), urinary metanephrines and neurotrophins, as well as validated symptom assessment for stress,

Correspondence to: Ariana L. Smith, Ariana.smith@uphs.upenn.edu.

This work has been presented at Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) American Urologic Association (AUA).

Compliance with ethical standards

Conflict of interest LH, DWF and MDS declare that they have no conflict of interest.

anxiety, depression, and bladder dysfunction at baseline and during, and following an acute laboratory stressor, the Trier Social Stress Test (TSST).

Results—Baseline measures of cortisol reactivity measured by CAR showed blunted response among women with OAB ($p = 0.015$), while cortisol response to the TSST was greater in the OAB group ($p = 0.019$). Among OAB patients, bladder urgency as measured by visual analog scale (VAS) increased from pre- to post-TSST ($p = 0.04$). There was a main effect of TSST on HR ($p < 0.001$), but no group interaction.

Conclusions—Preliminary findings suggest that women with OAB have greater physiologic and psychologic stress reactivity than healthy controls. Importantly for women with OAB, acute stress appears to exacerbate bladder urgency. Evaluation of the markers of stress response may suggest targets for potential diagnostic and therapeutic interventions.

Keywords

Overactive bladder; Cortisol; Stress; Hypothalamic–pituitary–adrenal axis

Introduction

The International Continence Society has defined overactive bladder (OAB) as urgency of urination, with or without urgency urinary incontinence, usually accompanied by frequency and nocturia [1, 2]. OAB is associated with substantial impairment in quality of life [3–5], with an economic burden of more than US\$65 billion/year [6]. Standard therapy for OAB is often disappointing due to marginal response rates to treatment, high rates of side effects, and low rates of persistence on therapy [7]. Major gaps in our understanding of the pathophysiology of OAB limit novel treatment development. The etiology of OAB remains elusive but appears to be multifactorial.

Comorbid psychiatric disease states, such as anxiety, depression, and stress disorders, are common among patients with OAB [8–11] and can complicate the understanding of OAB pathophysiology. Preclinical studies emphasize the importance of stress-sensitive connections between Barrington's nucleus, which plays a central role in the brainstem's control over micturition, and peripheral innervation of the urinary bladder [12]. Barrington's nucleus neurons extensively express the stress-related neuropeptide, corticotropin-releasing factor (CRF), but not its receptor in its spinal projections that regulate the micturition reflex [13, 14]. Moreover, many stressors upregulate CRF messenger RNA (mRNA) expression in Barrington's nucleus [15–17], and partial bladder outlet obstruction—a precipitator of OAB—has also been found to upregulate CRF mRNA in Barrington's nucleus [18]. Rodent models of social stress provide a greater mechanistic assessment of the interplay between hypothalamic–pituitary–adrenal axis (HPA-A) activation, and function of pelvic organs but are limited in their face validity when considering the complexity of psychosocial stress, HPA-A function, and voiding behaviors in humans [19–21]. Several human studies have confirmed that aversive psychosocial conditions including anxiety, depression, and stress states are common among men and women with OAB and other lower urinary tract symptoms (LUTS) [8–11, 22]; however, the directionality of this relationship is not entirely clear and may differ between men and women. While the prevalence of OAB among

individuals >40 years is similar for both men (16 %) and women (16.9 %) and increases for both sexes with advancing age [5], the role of stress activation of HPA-A function in the pathophysiology of OAB may be more relevant for women. Compared with men, women are at greater risk for affective disorders, which have been associated in some studies with HPA-A dysregulation [23, 24]. Ovarian hormone fluctuation and deprivation during peri- and postmenopause impacts HPA-A function, neurotransmitters involved in micturition control, and lower urinary tract musculature in a manner that may contribute to risk for LUTS among women [25]. Urinary markers of stress response, including metanephrines and neuropeptides, may serve as identifiable links in brain–bladder connection and warrant exploration.

Referable to these points, we sought to determine whether acute social stress activation of the HPA-A as measured by salivary cortisol levels during performance of the Trier Social Stress Test (TSST) would be greater in menopausal women with OAB compared with healthy controls. We also sought to test the hypothesis that levels of perceived stress during the TSST would be associated with exacerbation of LUTS in women with OAB compared with controls. We chose to focus on women without psychiatric diagnoses in order to minimize the confounders of mental illness on outcomes of interest.

Materials and methods

Participants

Postmenopausal women age 45–75 years diagnosed with OAB were recruited from a tertiary care urology practice. Age-matched healthy controls were recruited from an affiliated women's wellness center. Participants were excluded if they were undergoing treatment for stress reduction; using anxiolytic, hormonal, or antidepressant medications; or reported acute or chronic pain, urinary tract infection, bladder cancer, neurologic, or psychiatric disease. The Institutional Review Board approved this project; all participants gave written informed consent and were paid for their participation.

Eligible participants completed a baseline visit that included clinical assessment and validated questionnaires. An experienced interviewer assessed psychiatric disorders with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID) and excluded participants with identifiable conditions. Eligible participants returned within 2 weeks for visit 2 with salivary samples to measure baseline cortisol awakening response (CAR). During visit 2, participants took the TSST, submitted additional salivary samples for cortisol assessment, and urine samples for urinary catecholamine metabolites (metanephrine, normetanephrine) and neuropeptides [nerve growth factor (NGF); brain-derived neurotrophic factor (BDNF)], and completed additional questionnaires. All participants received follow-up phone calls 1, 3, and 7 days later.

Stress induction procedure

The TSST reliably induces moderate psychological stress, increases peripheral cortisol levels (salivary and blood), and is a well-validated tool for psychobiological research [26]. The TSST protocol consists of several components, including an anticipatory period, public

speaking, and mental arithmetic, all of which contribute to physiological response in HPA-A activity that varies depending on the population studied. Experimental sessions were run between 3 p.m. and 4 p.m. to control for circadian fluctuations in cortisol. All participants refrained from smoking, exercise, meals, alcohol, and soft drinks at least 1 h prior to testing. After arrival, urine and salivary samples were obtained and blood pressure and heart-rate measured. Patients rested for 30 min after arrival. Salivary samples were obtained T-15 and T-5 min prior to starting the TSST. At T=0, participants were introduced to the task they would perform. They were led into a room with three persons in white lab coats sitting at a table with video camera and tape recorder present. They were instructed that after a 10-min period of preparation, they would stand in front of the room and give a 5-min speech to convince the committee to hire them for a job. The committee was introduced as experts in nonverbal behavior, and participants were told that audio and video analysis of their interview would be performed. They were then given 10 min to prepare before being escorted back to the committee to begin their speech. If the participant ended before 5 min, they were told they had more time and asked to continue. When 5 min was up, the participant was asked to serially subtract 13 from 1022 as fast and accurately as possible. With each error, the participant was instructed to restart from 1022. After 5 min, the task was stopped. Immediately upon completion of this task (T=+20), participants were escorted back to the quiet room, where additional cortisol samples were collected (T + 30, T + 40, T + 50) and questionnaires were completed.

Behavioral measures

Psychological questionnaires—Self-report questionnaires administered were the Adverse Childhood Experience Questionnaire (ACE) [27], the Beck Anxiety Inventory (BAI) [28], the State Trait Anxiety Inventory (STAI) [29], and the Perceived Stress Scale (PSS) [30]. The ACE provided data on childhood abuse, neglect, and household dysfunction. The BAI assessed both cognitive and physiological symptoms of anxiety in the past month. The STAI assessed trait anxiety, a persistent characteristic of the participant; and state anxiety, which referenced the present level of anxiety symptoms. The PSS assessed the degree to which situations were appraised as stressful. The STAI and PSS were administered both before and after the TSST.

Bladder symptom questionnaires—Bladder symptoms were assessed with the Overactive Bladder Questionnaire (OAB-q) that measures degree of bother from individual bladder complaints as well as health-related quality of life over the last month, and the International Consultation on Incontinence Questionnaire-Overactive Bladder (ICIQ-OAB), which quantifies bladder symptom severity. Acute changes in bladder symptoms were assessed with the visual analog scale (VAS) for urgency with a 10-point Likert scale to assess urinary urgency at the time of questionnaire administration. The timing of administration of the questionnaires and physiologic measures is shown in “Appendix 1.”

Physiologic measures

Salivary cortisol—Following the baseline visit, participants were given Salivettes (SalivaBio oral swab, Salimetrics, LLC Inc., State College, PA, USA) for at-home salivary cortisol collection to assess CAR. They were instructed to collect saliva for two mornings

before and the morning of their scheduled visit 2. Samples were collected immediately upon awaking and then 30, 45, and 60 min later without brushing their teeth, eating, drinking, or smoking. Samples were stored in the participants' freezers and brought to visit 2 for processing. Participants also provided saliva samples during the TSST at visit 2; serial saliva cortisol samples were collected prior to (T-15, T-5, T=0) and following T + 30, T + 40, T + 50 min) TSST. Salivettes were stored at -20 °C until analysis.

Heart rate—Participants wore a heart-rate monitor throughout the TSST study procedures. Heart rate was documented in beats per minute at the same time points for salivary cortisol collection.

Urinary catecholamines/neuropeptides—Urinary catecholamine metabolites (metanephrine and normetanephrine) and neuropeptides (NGF, BDNF) were measured using enzyme-linked immunosorbent assay (ELISA) on urine samples collected prior to and following TSST. Given the known density of sensory afferents in the bladder, we hypothesized that a common pathway of stress expression may involve urinary solutes. Catecholamines (byproducts of cortisol metabolism) and neuropeptides including NGF and BDNF previously shown to be elevated in some patients with OAB were measured [31].

Laboratory assays

Salivary cortisol—Salivary cortisol was measured using an antibody-coated tube by radioimmunoassay (RIA) with an interassay coefficient of variation (CV) of 8.2 % and intraassay CVof <5 % (Salimetrics).

Urinary catecholamine/neuropeptides—Concentrations of urinary metanephrine and normetanephrine were measured in parallel by ELISA (DLD DIAGNOSTIKA GmbH, Cat#EA614/192) according to the manufacturer's instruction. The assay was run using 96-well plates and 10 µl of urine from each patient. The optical density (OD) values were read at 450 nm within 10 min after stopping the reaction using a Biotek Synergy 2 plate reader (BioTek Instruments Inc., Winooski, VT, USA). BDNF and NGF levels were measured by ELISA (Promega Cat#G7611, Cat#G7630) using 100 µl of urine taken from participants before and after TSST. Concentration of catecholamine metabolites and neuropeptides in urine was normalized to the concentration of creatinine measured by ELISA (R & D Company Cat#KGE005) to allow comparisons across different urine concentrations. All urine samples were run in duplicate.

Statistical analysis

Data was checked for normality prior to analysis. Distributions of the main salivary outcome variables (CAR, salivary cortisol response to TSST) and urinary outcome variables (NGF, BDNF) were skewed and thus were log transformed prior to analysis. Nonparametric tests were used for other nonnormal variables. Bivariate correlation, chi-square, and independent sample *t* tests were used to examine group differences in demographic factors and outcome variables. A post hoc power calculation was conducted to detect change in salivary cortisol between time +50 and time -5 for the TSST given seven controls and 11 women with OAB. The standard deviation (SD) for this change was 0.48. Assuming a type I, alpha, error of

5 %, this study has 80 % power to detect a difference between the two groups in salivary cortisol change of 1 SD that is 0.48.

CAR was calculated as mean salivary cortisol for four time points (awakening, 30, 45, and 60 min later) for 3 consecutive days and analyzed for between-group differences using repeated measures analysis of variance (RM-ANOVA). Heart rate response to TSST was also analyzed using RM-ANOVA. With respect to the TSST, cortisol values for T-15 and T-5 were averaged to obtain a baseline cortisol level for each participant, and a linear mixed-effects model was used to calculate the slope of change in cortisol level across the TSST in each group. This method accounts for the correlation among women over time similar to the RM-ANOVA model; however, it assumes a linear trend for cortisol values from pre-to post-TSST and does not require imputation of missing values if a given cortisol sample was insufficient for quantification, and it has increased statistical power over the RM-ANOVA model. Data analyses were carried out using SPSS software, version 20 (SPSS Inc., Chicago, IL, USA) and Stata v14, (Stata Corporation, College Station, TX, USA).

Results

Participant characteristics

Eighteen participants signed consent; 11 women with OAB and seven controls completed the TSST and provided all questionnaires, salivary, and urine samples. Table 1 reports demographic information and measures. Women in the OAB group were significantly older ($p = 0.05$), had more years since their final menstrual period ($p = 0.04$), and had fewer years of education ($p = 0.02$) than women in the healthy control group. None of the participants were smokers. Seven were using anticholinergic bladder medications, which are not felt to impact the HPA-A response. Baseline SCID interviews confirmed lack of DSM-IV psychiatric disease in both groups. Baseline validated questionnaires demonstrated similar scores for ACE ($U = 31.5$, $p = 0.52$) and BAI ($U = 25.0$, $p = 0.58$) in both groups.

Validated bladder questionnaires confirmed OAB symptoms in participants and lack of symptoms in controls. Mean ICIQ-OAB symptom scores were greater in OAB patients than controls (9.27 ± 1.4 vs. 4.71 ± 2.6 , $p < 0.001$). Mean OABq symptom severity scale was also greater in OAB patients compared with controls (48.63 ± 21.05 vs. 17.14 ± 21.38 , $p = 0.007$), with higher scores indicating greater symptom bother. Median OABq HRQL scale was 74.4 [interquartile range (IQR) 46.4] in patients with OAB compared with 96.8 (IQR 7.2) in controls ($p = 0.003$), with higher scores indicating better HRQL. The OABq HRQL subscales measured coping behavior, concern, sleep, and impact on social activities, all of which were significantly worse in patients with OAB compared with controls.

CAR and TSST outcomes

Mean CAR at each time point across 3 days suggested a blunted CAR in women with OAB based on repeated-measures analyses ($p = 0.015$, Fig. 1). Figure 2a shows means and SDs for raw cortisol values by group for each time point during the TSST. With respect to salivary cortisol response to the laboratory stressor, we observed a significant group difference in the slope of change in cortisol across the TSST ($p = 0.019$). In the OAB group,

salivary cortisol increased linearly throughout the experiment (slope estimate 0.0045, $p < 0.001$), while women in the control group did not display a significant change in cortisol over the study (slope estimate 0.00039, $p = 0.773$) (Fig. 2b). There was a main effect of TSST for heart rate ($p < 0.0001$), but no between-group differences in the degree to which heart rate increased across the laboratory stressor ($p = 0.84$) (Fig. 3).

VAS scores for urinary urgency from pre- to post-TSST significantly increased among women with OAB ($p = 0.04$); there was no change in the control group. STAI-S showed no significant change pre- to post-TSST in either group ($p = 0.12$, Table 2).

No differences in urinary metanephrines were detected between groups at baseline or following TSST; repeated measures ANOVA of log-transformed data showed no main effect or group $\times$ time interaction ($p = 0.66$, Table 2). Despite the rise in salivary cortisol following TSST, no rise in urinary normetanephrines was detected overall ($p = 0.08$) or by group ($p = 0.19$). Log-transformed BDNF (pg/ml) was higher in controls ($M = 37.2$) than in OAB participants ($M = 2.7$) pre-TSST but not post-TSST; there was no significant between groups in BDNF change score ($p = 0.34$). Log -transformed NGF (pg/ml) did not show main effects or group $\times$ time interaction ($p = 0.14$).

Exploratory analyses

As exploratory analyses, percent change in salivary cortisol from minimum to maximum during the TSST was assessed in relation to psychological measures. Cortisol percent change was positively and significantly correlated with Beck Depression Inventory ($r = 0.58$, $p = 0.02$) and BAI score ($r = 0.69$, $p = 0.004$) at visit 2, or with STAI-S ($r = 0.51$, $p = 0.05$) following the TSST.

Discussion

In this first study to examine basal and stress-activated HPA-A function in women with OAB, we observed several biological and clinical differences between them and healthy controls, supporting our hypothesis that stress plays an important and understudied role in the pathophysiology and subjective experience of OAB. While basal HPA-A function reflected by the CAR was blunted in women with OAB compared with controls, the relatively greater and prolonged salivary cortisol response to the laboratory stressor and the accentuation of urinary urgency among women with OAB highlights a clinically meaningful relationship between stress responsivity and LUTS in these women. The dissociation between basal and stress-activated HPA-A function observed in the OAB group is not uncommon, as reported by Kudielka and Wüst [32]. Some previous, but not all, studies have shown that factors such as whether a collection morning be a work day or weekend, age, reproductive status, chronic stress, or noncompliance with collection instructions contribute to observed flattening of the CAR [32]. However, it would be unlikely that there were systematic differences between the OAB and control groups in our study to account for the finding of blunted CAR in the OAB group. Furthermore, blunted CAR in the context of heightened cortisol response to stress has been found in patients with posttraumatic stress disorder, suggesting common pathophysiologic mechanisms between OAB and anxiety disorders [22].

It is not surprising that both groups experienced a similar autonomic response to the stressful nature of the TSST, as the social-evaluative nature of the TSST robustly triggers the autonomic nervous system [26]. This finding and the similar ratings on the subjective measure of state anxiety after the TSST suggest that the procedure itself provoked anxiety in both groups equally and that autonomic response to stress in the OAB group is intact.

While there were differences HPA-A response between the groups, baseline measures of anxiety (BAI, STAI) were comparable, suggesting this response is not the result of an underlying psychosocial condition. Furthermore, women with OAB experienced greater exacerbation in urgency symptoms around the stressor when compared with their baseline and with the control group. In exploratory analyses, cortisol change with TSST was greatest in those who reported the greatest psychological stress during the laboratory stressor. Together, these results suggest that women with OAB may represent a population with increased physiologic and psychologic stress reactivity that may benefit from additional modalities of therapeutic intervention for treatment of their bladder symptoms. Further, stress reactivity in patients with OAB may be a testable measure that predicts response to standard OAB treatment, thus allowing phenotyping and selective intervention for patients who may be resistant to standard pharmacologic interventions. Behavioral interventions including stress reduction and mindfulness-based meditation may have biologic plausibility and provide patients with a nonpharmacologic treatment intervention to control a condition that may be with them for a lifetime.

Urinary catecholamines did not show elevated expression in either group following TSST, which may be due to timing of the measure and use of voided specimens that reflect all the urine produced since the last void. Further studies of urinary expression are needed to understand this relationship.

As mentioned, the sample size is an important limitation in this study, but the significance of these preliminary data suggest that this is an important avenue for continued investigation. Likewise, these data cannot be generalized to the entire population of women with OAB, as we limited our sample to those women without comorbid psychiatric disorders. As this was meant to be a proof of concept study, we believe that it was critical to reduce psychiatric factors that influence basal and stress-activated HPA-A function. Though the healthy control group was somewhat younger and more recently postmenopausal than the OAB group, both groups were hypogonadal, reducing the likelihood that age or time since final menstrual period played a significant role in our findings [33]. Similarly, the small but significantly higher educational attainment in the control group is unlikely to have contributed to our findings. A previous study examining the impact of education found that cortisol levels across the TSST session were on average greater among those with more, not less, education. We found no differences between groups during the post-TSST recovery, yet it was during the test that we observed the greatest difference between healthy controls and women with OAB [34].

Products of stress response including cortisol act on the central nervous system to produce physiologic response including elevated blood pressure and heart rate. The impact of these specific physiologic responses on the bladder remains unknown, but this study suggests a

link between cortisol activity and bladder urgency, which potentially may be driven by a greater cortisol reactivity to stress in women with OAB syndrome. This study warrants replications in a larger sample in which covariates can be adequately controlled.

Conclusion

Women with OAB have blunted baseline physiologic measures of cortisol as reflected in CAR and greater physiologic responsiveness to stress as measured by salivary cortisol following TSST. These findings add to our emerging understanding of the complex interactions among stress, HPA-A activity and OAB. Evaluation of markers of stress response may provide future targets for potential diagnostic and therapeutic interventions for the treatment of OAB.

Acknowledgments

Dina H. Appleby, M.S. for her statistical assistance.

Funding This work was funded by NIH/NIDDK O'Brien Urology Center Grant P50 DK052620-15, Penn Center for Women's Behavioral Wellness (NIH P50 MH099910, R01 AG048839, K24 DA030301, R01 DA037289).

ALS receives research grants from NIH and Allergan and honoraria from Gray's Anatomy. APM receives research grants from NIH and University of Colorado Department of Surgery. RV receives research grants from NIH, is an editorial board member for Elsevier, a Lecturer for SUFU, Drexel, University of Colorado, New York Medical College, and Rutgers, and an unpaid advisory board member for Brain and Behavioral Research Foundation, Society for Neuroscience and University of Michigan Health System. AJW is a consultant for Medtronic, Axonics and Allergan. CNE receives research grants from NIH and Shire, consults for Forest Laboratories, and has personal investments in Pfizer, Johnson and Johnson, Merck, Abbott, and Abbvie.

Appendix 1

Table 3

Timing of study procedures and questionnaires

Schedule of measures and procedures (T-0 defined as the start of the trier social stress test)	Baseline evaluation	visit 2
Physiologic measures		
Salivary cortisol awakening response (2 days prior to visit 2)	X	
Heart rate	X	Continuous from T-15 to T + 50
Salivary cortisol		T-15, T-5, T = 0, T + 30, T + 40. T + 50
Urinary metanephrines		T-15, T + 20 to 50
Urinary neuropeptides		T-15, T + 20 to 50
Procedures		
Informed consent	X	
Trier social stress test (TSST)		X
Questionnaires		
Structured clinical interview for DSM-IV Axis I disorders (SCID)	X	
Overactive bladder questionnaire (OAB-q)	X	
International consultation on incontinence questionnaire-overactive bladder (ICIQ-OAB).	X	

Schedule of measures and procedures (T-0 defined as the start of the trier social stress test)	Baseline evaluation	visit 2
Traumatic life events questionnaire (TLEQ)	X	
Adverse childhood experience (ACE) questionnaire	X	
Beck depression index	X	T-15
Beck anxiety inventory	X	T-15
Visual analog scales for urgency	X	T-15, T + 20, T + 50
Perceived stress scale		T-15, T + 20 to 50
State trait anxiety inventory	X	T-15, T + 20 to 50
Follow-up phone calls (Days 1, 3, and 7 from visit 2)		

References

- Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the international continence society. *Neurourol Urodyn.* 2002; 21:167–178. [PubMed: 11857671]
- Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, Monga A, Petri E, Rizk DE, Sand PK, Schaer GN. An international urogynecological association (IUGA)/international continence society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Int Urogynecol J.* 2010; 21(1):5–26. [PubMed: 19937315]
- Dmochowski RR, Newman DK. Impact of overactive bladder on women in the United States: results of a national survey. *Curr Med Res Opin.* 2007; 23(1):65–76. [PubMed: 17257467]
- Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I. The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. *BJU Int.* 2008; 101(11):1388–1395. [PubMed: 18454794]
- Stewart WF, Van Rooyen JB, Cundiff GW, Abrams P, Herzog AR, Corey R, Hunt TL, Wein AJ. Prevalence and burden of overactive bladder in the United States. *World J Urol.* 2003; 20(6):327–336. [PubMed: 12811491]
- Coyne KS, Wein A, Nicholson S, Kvasz M, Chen CI, Milsom I. Economic burden of urgency urinary incontinence in the United States: a systematic review. *J Manag Care Pharm.* 2014; 20(2): 130–140. [PubMed: 24456314]
- Brubaker L, Fanning K, Goldberg EL, Benner JS, Trocio JN, Bavendam T, Jumadilova Z. Predictors of discontinuing overactive bladder medications. *BJU Int.* 2010; 105(9):1283–1290. [PubMed: 19912189]
- Milsom I, Kaplan SA, Coyne KS, Sexton CC, Kopp ZS. Effect of bothersome overactive bladder symptoms on health-related quality of life, anxiety, depression, and treatment seeking in the United States: results from EpiLUTS. *Urology.* 2012; 80(1):90–96. [PubMed: 22748867]
- Kinsey D, Pretorius S, Glover L, Alexander T. The psychological impact of overactive bladder: a systematic review. *J Health Psychol.* 2014
- Bradley CS, Nygaard IE, Torner JC, Hillis SL, Johnson S, Sadler AG. Overactive bladder and mental health symptoms in recently deployed female veterans. *J Urol.* 2014; 191(5):1327–1332. [PubMed: 24316095]
- Vrijens D, Drossaerts J, van Koeveeringe G, Van Kerrebroeck P, van Os J, Leue C. Affective symptoms and the overactive bladder - a systematic review. *J Psychosom Res.* 2015; 78(2):95–108. [PubMed: 25499886]
- Valentino RJ, Wood SK, Wein AJ, Zderic SA. The bladder-brain connection: putative role of corticotropin-releasing factor. *Nat Rev Urol.* 2011; 8(1):19–28. [PubMed: 21135878]
- Valentino RJ, Chen S, Zhu Y, Aston-Jones G. Evidence for divergent projections to the brain noradrenergic system and the spinal parasympathetic system from Barrington's nucleus. *Brain Res.* 1996; 732(1–2):1–15. [PubMed: 8891263]

14. Vincent SR, Satoh K. Corticotropin-releasing factor (CRF) immunoreactivity in the dorsolateral Pontine tegmentum: further studies on the micturition reflex system. *Brain Res.* 1984; 308(2):387–391. [PubMed: 6383518]
15. Imaki T, Nahan JL, Rivier C, Sawchenko PE, Vale W. Differential regulation of corticotropin-releasing factor mRNA in rat brain regions by glucocorticoids and stress. *J Neurosci.* 1991; 11(3): 585–599. [PubMed: 2002354]
16. Imaki T, Vale W, Sawchenko PE. Regulation of corticotropin-releasing factor mRNA in neuroendocrine and autonomic neurons by osmotic stimulation and volume loading. *Neuroendocrinology.* 1992; 56(5):633–640. [PubMed: 1488095]
17. Wood SK, Baez MA, Bhatnagar S, Valentino RJ. Social stress-induced bladder dysfunction: potential role of corticotropin-releasing factor. *Am J Physiol Regul Integr Comp Physiol.* 2009; 296(5):R1671–R1678. [PubMed: 19279290]
18. Wood SK, McFadden K, Griffin T, Wolfe JH, Zderic S, Valentino RJ. A corticotropin-releasing factor receptor antagonist improves urodynamic dysfunction produced by social stress or partial bladder outlet obstruction in male rats. *Am J Physiol Regul Integr Comp Physiol.* 2013; 304(11):R940–R950. [PubMed: 23552576]
19. Smith AL, Leung J, Kun S, Zhang R, Karagiannides I, Raz S, Lee U, Glovatscka V, Pothoulakis C, Bradesi S, Mayer EA, Rodriguez LV. The effects of acute and chronic psychological stress on bladder function in a rodent model. *Urology.* 2011; 78(4):967.e961–967.e967. [PubMed: 21868072]
20. McGonagle E, Smith A, Butler S, Sliwoski J, Valentino R, Canning D, Zderic SA. Water avoidance stress results in an altered voiding phenotype in male mice. *Neurourol Urodyn.* 2012; 31(7):1185–1189. [PubMed: 22473515]
21. Mingin GC, Peterson A, Erickson CS, Nelson MT, Vizzard MA. Social stress induces changes in urinary bladder function, bladder NGF content, and generalized bladder inflammation in mice. *Am J Physiol Regul Integr Comp Physiol.* 2014; 307(7):R893–R900. [PubMed: 25100077]
22. Luo H, Hu X, Liu X, Ma X, Guo W, Qiu C, Wang Y, Wang Q, Zhang X, Zhang W, Hannum G, Zhang K, Liu X, Li T. Hair cortisol level as a biomarker for altered hypothalamic-pituitary-adrenal activity in female adolescents with posttraumatic stress disorder after the 2008 Wenchuan earthquake. *Biol Psychiatry.* 2012; 72(1):65–69. [PubMed: 22305287]
23. Bangasser DA. Sex differences in stress-related receptors: “micro” differences with “macro” implications for mood and anxiety disorders. *Biol Sex Differ.* 2013; 4(1):2. [PubMed: 23336736]
24. Bremner MA, Deeg DJ, Beekman AT, Penninx BW, Lips P, Hoogendijk WJ. Major depression in late life is associated with both hypo- and hypercortisolemia. *Biol Psychiatry.* 2007; 62(5):479–486. [PubMed: 17481591]
25. Kwon JK, Kim JH, Choi H, Chang IH, Park BR, Kwon SS, Lee ES, Choi GY, Lee JJ, Lee IS. Voiding characteristics and related hormonal changes in peri-menopausal and post-menopausal women: a preliminary study. *Maturitas.* 2014; 79(3):311–315. [PubMed: 25150899]
26. Kirschbaum C, Pirke K-M, Hellhammer DH. The ‘trier social stress test’ - a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology.* 1993; 28:76–81. [PubMed: 8255414]
27. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The adverse childhood experiences (ACE) study. *Am J Prev Med.* 1998; 14(4):245–258. [PubMed: 9635069]
28. Beck, AT.; Steer, RA. Beck anxiety inventory manual. San Antonio, TX: Psychological Corporation; 1993.
29. Spielberger, CD.; Gorsuch, RL.; Lushene, PR.; Vagg, PR.; Jacobs, AG. Manual for the state-trait anxiety inventory (form Y). Palo Alto: Consulting Psychologists Press, Inc.; 1983.
30. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav.* 1983; 24(4):385–396. [PubMed: 6668417]
31. Cruz CD. Neurotrophins in bladder function: what do we know and where do we go from here? *Neurourol Urodyn.* 2014; 33(1):39–45. [PubMed: 23775873]

32. Kudielka BM, Wust S. Human models in acute and chronic stress: assessing determinants of individual hypothalamus-pituitary-adrenal axis activity and reactivity. *Stress (Amst, Neth)*. 2010; 13(1):1–14.
33. Kudielka BM, Buske-Kirschbaum A, Hellhammer DH, Kirschbaum C. HPA axis responses to laboratory psychosocial stress in healthy elderly adults, younger adults, and children: impact of age and gender. *Psychoneuroendocrinology*. 2004; 29(1):83–98. [PubMed: 14575731]
34. Fiocco AJ, Joobor R, Lupien SJ. Education modulates cortisol reactivity to the trier social stress test in middle-aged adults. *Psychoneuroendocrinology*. 2007; 32(8–10):1158–1163. [PubMed: 17920776]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 1.
Mean cortisol awakening response over 3 days in patients and controls. *Error bars* represent 1 standard error (SE)

Fig. 2.

a Mean salivary cortisol response over time in women with overactive bladder (OAB) and controls undergoing the Trier Social Stress Test (TSST): *T0* initiation of TSST. *Error bars* represent 1 standard error (SE). **b** Slope of change in salivary cortisol in women with overactive bladder (OAB) and controls from baseline to post-Trier Social Stress Test

Fig. 3.

Heart-rate response in patients and controls during acute stressor: *T0* initiation of Trier Social Stress Test (TSST). *Error bars* represent 1 standard error (SE)

Table 1

Participant characteristics and measures

Characteristics	Control (<i>n</i> = 7)	OAB (<i>n</i> = 11)	<i>P</i> value
Age	56.29 (3.9)	63.55 (8.3)	0.05 *
Weight	180.64 (47.5)	175.45 (44.4)	0.82
Years education	16.71 (1.5)	14.45 (2.1)	0.02 *
Race (<i>n</i>)			0.31
Caucasian	5	4	
Non-Caucasian	2	7	
Marital status (<i>n</i>)			0.36
Married	5	5	
Single, divorced, widowed	2	6	
Years since menopause	4.33 (3.2)	12.0 (7.86)	0.04 *
Measures	Control (<i>n</i> = 7)	OAB (<i>n</i> = 11)	<i>P</i> value
ACE	2 [4]	2 [3]	0.52
BAI			
Baseline	2.0 [14.0]	4.0 [8.0]	0.58
Visit 2 Pre-TSST	2.0 [12.0]	3.0 [5.0]	0.58
STAI-trait	25.14 (13.35)	32.91 (11.77)	0.21
PSS	7.57 (6.63)	10.55 (8.91)	0.46
OABq			
Symptom scale	17.14 (21.38)	48.64 (21.05)	<0.01 *
HRQL	96.8 [7.2]	74.4 [46.4]	<0.01 *
ICIQ-OAB	4.71 (2.56)	9.27 (1.35)	<0.01 *
CAR			0.015 *
Awakening	0.56 (0.45)	0.26 (0.15)	
Awakening +30	0.67 (0.36)	0.35 (0.22)	
Awakening +45	0.49 (0.13)	0.30 (0.18)	
Awakening +60	0.49 (0.23)	0.26 (0.15)	
Slope of salivary cortisol TSST	0.00039	0.0045	0.019 *

For normally distributed data, mean (standard deviation) is reported, with corresponding *p* value for parametric statistical test. For nonnormally distributed data, median [interquartile range] is reported, with corresponding *p* value for nonparametric statistical test

ACE adverse childhood experience, *AUCi* area under curve to increase, *BAI* Beck Anxiety Inventory, *CAR* cortisol awakening response, *HRQL* Health Related Quality of Life, *ICIQ-OAB* International Consultation on Incontinence Questionnaire–Overactive Bladder, *OABq* Overactive Bladder questionnaire, *PSS* Perceived Stress Scale, *STAI* State Trait Anxiety Inventory, *TSST* Trier Social Stress Test, *VAS* visual analog scale

* Statistically significant

Table 2

Participant measures pre- and post-Trier Social Stress Test (TSST)

	Control (<i>n</i> = 7)			OAB (<i>n</i> = 11)			<i>P</i> value
	Pre-TSST	Post-TSST		Pre-TSST	Post-TSST		
STAI-State	21.0 [15.0]	27.14 (7.80)		31.0 [23.0]	35.0 (14.16)		0.12
VAS urgency	1.29 (2.22)	1.57 (3.05)		0.82 (1.25)	2.82 (2.89)		0.04*
Laboratory urine measures (log value and referenced to urinary creatinine)							
BDNF	7.85 [95.8]	10.59 [37.73]		0.93 [3.07]	2.45 [3.10]		0.34
NGF	0.0 [4.47]	1.49 [12.86]		0.0 [1.12]	0.0 [0.25]		0.14
Metanephrine	1.52 [2.07]	1.17 [0.82]		1.26 [1.20]	1.09 [1.0]		0.66
Normetanephrine	4.50 [3.52]	3.17 [1.48]		3.39 [1.24]	3.43 [1.15]		0.19

For normally distributed data, mean (standard deviation) is reported, with corresponding *p* value for parametric statistical test. For nonnormally distributed data, median [interquartile range] is reported. *P* values for interaction term

BDNF/brain-derived neurotrophic factor, *NGF*/nerve growth factor, *STAI*/State Trait Anxiety Inventory, *TSST*/Trier Social Stress Test, *VAS* visual analog scale