Stress Induced Hypothalamus-Pituitary-Adrenal Axis Responses and Disturbances in Psychological Profiles in Men With Chronic Prostatitis/Chronic Pelvic Pain Syndrome

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Purpose: Chronic pelvic pain in men has a strong relationship with biopsychosocial stress and central nervous system sensitization may incite or perpetuate the pain syndrome. We evaluated patients and asymptomatic controls for psychological factors and neuroendocrine reactivity under provoked acute stress conditions.

Materials and Methods: Men with pain (60) and asymptomatic controls (30) completed psychological questionnaires including the Perceived Stress, Beck Anxiety, Type A behavior and Brief Symptom Inventory for distress from symptoms. Hypothalamic-pituitary-adrenal axis function was measured during the Trier Social Stress Test with serum adrenocorticotropin hormone and cortisol reactivity at precise times, before and during acute stress, which consisted of a speech and mental arithmetic task in front of an audience. The Positive and Negative Affective Scale measured the state of emotions.

Results: Patients with chronic pelvic pain had significantly more anxiety, perceived stress and a higher profile of global distress in all Brief Symptom Inventory domains ($p < 0.001$), scoring in the 94th vs the 49th percentile for controls (normal population). Patients showed a significantly blunted plasma adrenocorticotropin hormone response curve with a mean total response approximately 30% less vs controls ($p = 0.038$) but no differences in any cortisol responses. Patients with pelvic pain had less emotional negativity after the test than controls, suggesting differences in cognitive appraisal.

Conclusions: Men with pelvic pain have significant disturbances in psychological profiles compared to healthy controls and evidence of altered hypothalamic-pituitary adrenal axis function in response to acute stress. These central nervous system observations may be a consequence of neuropsychological adjustments to chronic pain and modulated by personality.

Key Words: prostatitis; pelvic pain; hydrocortisone; stress disorders, traumatic, acute

Abbreviations and Acronyms

ACTH = adrenocorticotropin hormone

BSI = Brief Symptom Index

CPPS = chronic pelvic pain syndrome

CV = coefficient of variation

GSI = Global Severity Index

HPA = hypothalamus-pituitary-adrenal

NIH-CPSI = National Institutes of Health-Chronic Prostatitis Symptom Index

PANAS-X = Positive and Negative Affect Scale

TSST = Trier Social Stress Test

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For another article on a related topic see page 2483.

STRESS is common in men with chronic prostatitis/chronic pelvic pain syndrome and has been implicated in the initiation or exacerbation of the syndrome.[1–3] Chronic pain can be considered a form of chronic stress. One of the best known stress related endocrine reactions is the hormonal release through the hypothalamus-pituitary-adrenal axis. It has been proposed as a common pathway possibly linking antecedent factors such as personality disorder, stress and immunological disturbances.[4] Functional and structural adaptations

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within the HPA axis, suggestive of long-term alterations in neuroendocrine reactivity to subsequent stressors, can be elicited by chronic stress.

Patients with chronic pain have disturbances of the HPA axis as demonstrated in disorders such as fibromyalgia,[4,5] chronic fatigue syndrome,[5,6] posttraumatic stress disorder and chronic pelvic pain in women.[7] We have reported an augmented cortisol awakening response in men with CPPS indicative of HPA dysfunction.[8] In this study we compared psychological factors and HPA reactivity to acute stress in men with CPPS and controls.

PATIENTS AND METHODS

Patients

Men referred to the Stanford University Urology Clinic from December 2005 to July 2008 with symptoms of chronic prostatitis/CPPS, NIH category III, for at least 3 months within the last 6 months were invited to participate in the study. Patients were 18 years old or older, had a total score on the NIH-CPSI of 12 or greater (scale of 0 to 43) and a nonzero score pain domain at study enrollment.[9] They had no history of conditions known to affect the HPA axis including fibromyalgia, chronic fatigue syndrome or posttraumatic stress disorder. Healthy male volunteers with no history of genitourinary disease or symptoms, matched for age, were recruited by advertisement as the control group. The protocol was reviewed and approved by the University institutional review board. Subjects gave informed consent and were paid for participation. Subject demographics and CPPS disease history were obtained.

Symptom and Psychometric Assessments

The NIH-CPSI and the Pelvic Pain Symptom Score were used to screen participants and repeated immediately before acute stress testing to confirm active pelvic pain in the CPPS cohort.[10] Baseline assessments to evaluate subject psychological profiles and psychosocial stress were done in the week before the experimental acute stress test. Psychological state was measures with the BSI, which scores 9 primary symptom dimensions including depression, anxiety, somatization, obsessive-compulsive behavior, interpersonal sensitivity, hostility, phobic activity, paranoid ideation, and psychoticism, and an overall measure of distress, the GSI of the BSI.[11] The validated BSI lists problems a patient may have and queries how much the problem has distressed them during the last 7 days. Responses are a 5-point Likert scale of 0 (not at all) to 4 (extremely bothersome). The Beck Anxiety Inventory measures symptoms of anxiety, which are minimally shared with depression.[12] The Bortner Type A Personality Test categorizes personality based on response to stress.[13] The Perceived Stress Scale measures perception of stress, feelings and thoughts during the last month.[14] The Perceived Stress Scale assesses unpredictability, lack of control and burden overload, and includes direct inquiries about current levels of stress. State of emotions before and after the acute stress was measured with a PANAS-X, and an adjective list of positive and negative emotions (Likert-type scale of 1 to 5).[15]

Experimental Stress Protocol

Subjects participated in the Trier Social Stress Test.[16,17] The validated TSST is a standardized protocol for induction of moderate cognitive and social stress in a laboratory setting to evaluate effects on physiological responses (activation of the HPA axis).[16] The protocol consisted of an anticipatory period followed by a 10-minute test during which the subject delivers a monologue speech about his qualifications for an advertised job and then performs an arithmetic task of mental calculation reciting serial subtraction from 989 by 15s in front of a panel of 3 evaluators. The panel provides no feedback. Sessions were videotaped, and subjects were informed that their unconscious body language and content of presentations would be analyzed. We conducted the TSST in the Stanford General Clinical Research Center between 3:00 and 4:00 p.m. because previous research has shown that HPA axis responses, reflected in greater cortisol changes for stress responses, are greater in the late afternoon.[17] Participants could not smoke, drink alcohol or exercise 1 hour before arriving for the TSST and had to be medication-free on the test day.

The TSST procedures required precise timing. An intravenous line was inserted 30 minutes before the TSST. Baseline blood samples were collected via intravenous access and saliva samples in sterile capped plastic Salivette tubes (Starstedt Inc., Newton, North Carolina) with cotton swabs. Sample collections were at 10 times, -30 minutes and 0 minutes before the TSST, after preparation for the speech (10 minutes), before and after the speech (0, 5 minutes), after the mental arithmetic task (5 minutes), and in the recovery period after completion of the TSST (10, 20, 40 and 60 minutes) during which time participants were instructed to sit quietly.

Blood and Saliva Biochemical Analysis

Plasma ACTH, serum cortisol and salivary cortisol were analyzed to assess HPA axis response to stress. Serum cortisol levels reflect cortisol bound to protein as well as biologically active, free (unbound) cortisol. Cortisol in salivary samples reflects only the free fraction of cortisol in plasma.[18] Immediately after collection blood samples were centrifuged at 3,000 rpm for 10 minutes and serum was stored at −70C. Total serum cortisol and ACTH in ethylenediaminetetraacetic acid plasma were assayed in duplicate using radioimmunoassay (DiaSorin, Stillwater, Minnesota). The minimum detectable cortisol concentration was 0.21 μg/dl, and the intra-assay and interassay CVs were less than 7.7% and 9.8%, respectively. The minimum detectable ACTH concentration was 15 pg/ml and intra-assay and interassay CVs were less than 9.0% and 6.7%, respectively.

Saliva samples were stored at −70C before centrifugation (3,000 rpm, 10 minutes) and analysis of cortisol with time resolved luminescence immunoassay reagents (Immuno-Biological Laboratories, Inc., Hamburg, Germany).[19] Assay sensitivity was 0.015 μg/dl. Intra-assay and interassay CVs were less than 10%. All assays were performed by the General Clinical Research Center laboratory and samples col-