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Gender determines ACTH recovery from hypercortisolemia in healthy older humans

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ABSTRACT

Objective. Available clinical data raise the possibility that stress-adaptive mechanisms differ by gender. However, this notion has not been rigorously tested in relation to cortisol-mediated negative feedback.

Materials/Methods. Degree of ACTH inhibition during and recovery from an experimental cortisol clamp was tested in 20 healthy older subjects (age 60 ± 2.2 y). Volunteers received oral placebo or ketoconazole (KTCZ) to inhibit adrenal steroidogenesis along with i.v. infusions of saline or a low vs high physiological dose of cortisol in a prospectively randomized double-blind, placebo-controlled design. ACTH and cortisol concentrations were measured every 10 min during the feedback-clamp phase and thereafter (recovery or escape phase). Corticosteroid-binding globulin (CBG) was measured, and free cortisol concentrations were calculated.

Results. Gender did not determine mean ACTH concentrations during the saline or cortisol feedback-clamp phases per se. However, women had markedly impaired ACTH recovery after stopping both low- and high-dose cortisol infusions compared with men ($P = 0.005$, KTCZ/low-dose cortisol arm; and $P = 0.006$, KTCZ/high-dose cortisol arm). Decreased ACTH recovery in women was accompanied by lower total and free cortisol concentrations, pointing to heightened feedback inhibition of hypothalamo-pituitary drive of ACTH secretion as the main mechanism.

Conclusions. In summary, gender or a factor related to gender, such as sex steroids or body composition, determines recovery of ACTH secretion from cortisol-enforced negative feedback. Attenuated ACTH recovery in post-menopausal women may have relevance to sex differences in stress-related adaptations.

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1. Introduction

Time-delimited stress-adaptive responses of the corticotropic axis are critical to sustain life and regulate key metabolic processes [1]. Hypothalamo-pituitary responses are activated and restrained by feedforward and feedback signals, which together mediate homeostatic ACTH fluctuations in patho-physiological states [2–5]. Albeit crucial to multicomponent

Abbreviations: ACTH, adrenocorticotropic hormone; E_2, estradiol; T, testosterone; KTCZ, ketoconazole; CRH, corticotropin-releasing hormone; AVP, arginine vasopressin.

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regulation in neuroendocrine systems, feedback regulation is less well studied than feedforward drive [6,7]. Moreover, how gender, sex steroids, puberty, hypogonadism and aging supervise feedback effects is largely unknown [8–10]. In particular for the stress axis, whereas gender and sex steroids regulate ACTH secretion strongly in animals, investigations in human subjects are both limited and discrepant [11].

In the rodent, female sex (and estradiol) and male sex (and testosterone) respectively potentiate and attenuate stress responses [1,12,13]. However, in the human, inferences on the role of gender in modulating hypothalamic-pituitary-adrenal (HPA) responses are inconsistent. In part, inconsistencies may reflect the dose and type of feedback signal applied (e.g. long-lived synthetic glucocorticoids or physiological cortisol), as well as confounding interactions among gender, age and the degree and type of stress [5,14–16]. In an initial effort to address these uncertainties, the present clinical investigation examines, in a given age group, how gender impacts (a) feedback inhibition of ACTH secretion by varying systemic cortisol concentrations; and (b) feedforward recovery of hypothalamo-pituitary drive of ACTH secretion during subsequent hypocortisolemia. These issues are important, since the short-term consequences of blunted cortisol/ACTH feedback include elevated glucocorticoid secretion and heightened ACTH responsiveness to CRH and AVP, while the long-term consequences of excessive ACTH/cortisol feedforward include elevated blood pressure, suppressed immune function, impaired insulin action, visceral-fat accumulation, decreased muscle protein and bone mass, and possibly reduced memory and hippocampal neurogenesis [17–20]. Thus, understanding how gender regulates ACTH secretion in older adults should provide insights into stress-adaptive mechanisms in individuals at increased risk of frailty, injury and disability.

2. Materials and methods

2.1. Overview

The basic postulate tested was that older men and postmenopausal women differ in the degree of feedback inhibition of ACTH secretion by, and subsequent escape of ACTH secretion from, controlled intravenous cortisol exposure and withdrawal. This was an institutional review board-approved, prospectively randomized, double-blind, and placebo-controlled crossover study. The investigational protocol was also reviewed by the U.S. Food and Drug Administration and assigned an investigator new drug number, inasmuch as ketoconazole (KTCZ) was used off-label to block adrenal steroidogenesis reversibly [21,22].

2.2. Subjects

Participants were recruited from the community within the allowable age range of 50–80 years. Ten men and ten women were enrolled. Women were postmenopausal by 2 yr or more. No volunteers were receiving hormone replacement. Subjects maintained conventional work and sleeping patterns and reported no recent (within 10 days) transmeridian travel, significant (≥2 kg) weight change, psychosocial stress, substance abuse, neuropsychiatric medications or illness, or systemic disease. There were no concurrent or historical neuropsychiatric diagnoses or related drug treatments, and no disorders of eating, behavior, anxiety, depression or psychosis, when assessed as in earlier cortisol feedback studies [23]. A complete medical history, physical examination, and screening tests of hematological, renal, hepatic, metabolic and endocrine function were normal.

Volunteers were admitted to the Mayo Center for Translational Science for 4 separate inpatient overnight study sessions, each separated by at least 10 days. The study was double blind, using oral placebo vs KTCZ capsules, and i.v. saline vs cortisol infusions. (We did not try to infuse cortisol under oral placebo, since the levels would then be hard to interpret under high uninhibited cortisol pulses). Overnight infusions and next-morning sampling were chosen to examine gender-related regulation of the strong diurnal rise in ACTH in the cortisol-feedback paradigm. Lights were extinguished at 2000 h. Subjects received either oral placebo tablets or KTCZ pills (600 mg in men and 400 mg in women) at 1800 h. KCTZ was given with a nondairy snack to obviate dyspepsia. The dose was selected in pilot studies to achieve comparable suppression of cortisol in the two sexes. KTCZ (at one-half the dose) or placebo was given again at 2200 h and 0600 h to continue to block adrenal steroidogenesis. Concurrently, either saline (100 mL) or cortisol (as hydrocortisone succinate in saline 100 mL) at a total dose of 2.5 mg/m^2 (low dose) or 10 mg/m^2 (high dose) was infused continuously i.v. over 8 h until 0200 h. This created 4 separate cortisol clamps (treatment arms): 1) placebo + saline addback; 2) KTCZ + saline addback; 3) KTCZ + low-dose cortisol (LDC) infusion; and 4) KTCZ + high-dose cortisol (HDC) infusion (Fig. 1). Blood samples were obtained for later measurement of plasma ACTH (1.0 mL) and serum cortisol (0.5 mL) every 10 min for 14 h from 2200 h until 1200 h the next day. Subjects slept through the sampling until 0600 h. Fourteen h of sampling was to monitor ACTH secretion during the last 4 h of the constant 8-h infusion clamp, and for 10 additional h after stopping i.v. cortisol or saline abruptly at 0200 h. At 1200 h, 25 mg hydrocortisone succinate was administered as an i.v. bolus for safety reasons.

2.3. Hormone assays

Plasma ACTH was assayed via a highly sensitive and specific, solid-phase sequential immunoassay (Siemens Healthcare Diagnostics, Deerfield, IL). The detection threshold was 5 ng/L (to convert to SI units, divide by 4.5). The intra-assay coefficient of variations (CV) were 6.4%, 2.7%, and 3.2% at 5.7 ng/L, 28 ng/L, and 402 ng/L, respectively. Cortisol was assayed via competitive binding immunoenzymatic assay (Beckman Coulter, Inc., Fullerton CA). The detection limit was 0.4 μg/dL (to convert to SI units, multiply by 27.6) and intra-assay CVs were 13%, 9.4%, and 6.6% at 1.6 μg/dL, 2.8 μg/dL, and 30 μg/dL, respectively. All samples from a given subject were assayed in the same batch. Sex steroids were assayed by mass spectrometry, and LH, FSH, TSH and prolactin by immunochemiluminescence [24,25].

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