

GENDER DIFFERENCES IN SENSITIVITY OF THE
HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL AXIS TO
STRESS-LIKE STIMULATION

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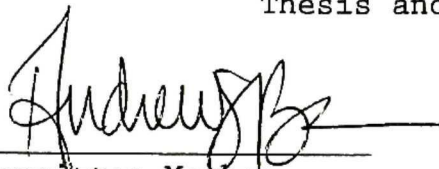
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A handwritten signature in cursive script, appearing to read "William T. Gallucci".

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ABSTRACT

Title of Thesis: Gender Differences in sensitivity of the
Hypothalamic-Pituitary-Adrenocortical
axis to stress-like stimulation

William T. Gallucci, Masters of Science, 1991

Thesis directed by: Andrew Baum, Ph.D.
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Possible sex differences in the sensitivity of the hypothalamic-pituitary-adrenal (HPA) axis, a major component of the stress response, was examined. We initially studied 24 healthy men and 19 healthy women by administering a corticotropin-releasing hormone (CRH) stimulation test. Each subject was given a bolus injection of ovine CRH at 8:00 P.M. when the HPA axis is normally quiescent, and serial blood samples were taken over a two-hour session. Plasma adrenocorticotrophic hormone (ACTH) responses to oCRH were significantly greater among women than among men. In contrast, cortisol concentrations were similar in both groups, albeit somewhat more prolonged in women. To examine the status of the adrenal cortices, five healthy men and five healthy women underwent a series of ACTH stimulation tests in which graded doses of synthetic

ACTH were administered and plasma cortisol concentrations were measured. There were no differences between men and women in the ACTH-cortisol dose response curves. These findings suggest that although healthy women produce more ACTH compared with healthy men in response to the same hormonal stimulus, they have similar adrenal responses to ACTH. Central corticotropin-releasing activity may be different between men and women and such differences in the central stress response might be implicated in the known epidemiological differences of diseases of stress system dysregulation between men and women.

GENDER DIFFERENCES IN SENSITIVITY OF THE
HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL AXIS TO
STRESS-LIKE STIMULATION

by

William T. Gallucci

Thesis submitted to the faculty of the Department of
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Dedication

I wish to dedicate this work to my children, Bill and Criss Gallucci, who have been a source of support and inspiration and who reluctancy at times did without my company so the clinical research presented here could progress. Knowledge is not without cost, and I thank them.

Acknowledgement

I wish to thank Drs. Philip Gold, Mitchel Kling and George Chrousos for their guidance, training, and access to the volunteers, whose data is presented in this work. In addition, I wish to thank Dr. Laue for access to her patients, and finally, I would like to thank Dr. Baum for guiding this thesis, correcting and overseeing my writing and providing insights to a wealth of stress data, which in turn has spawned several scientific projects.

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INTRODUCTION

Men and women appear to differ in how they respond during acute stress and these differences have been interpreted to influence susceptibility to disease and capacity to cope during severe or sustained stress. Research has indicated that men exhibit larger increases in blood pressure and higher levels of catecholamines during or immediately after an acute stressor such as a laboratory challenge (e.g., Dembroski et al., 1985; Frankenhaeuser et al., 1976; Johansson and Post, 1974; Stoney et al., 1987). Heart rate and subjective ratings of stress tend to show the opposite: Women exhibit larger heart rate increases during or after challenge and report more distress than do men (Frankenhaeuser, 1978; Stoney et al., 1987). Although relatively little data are available regarding the possibility of sex differences in cortisol responses in humans during or after stress, in one study men were found to have larger increases in cortisol than did women after performing a mental task (Collins and Frankenhaeuser, 1978). Moreover, psychiatric illnesses associated with significant hypercortisolism, including major depression and anorexia nervosa, are significantly more common in women than in men (Gold et al., 1988; Weissman, 1977).

There are few studies of sex differences in cortisol response during stress among humans. In animal studies on the other hand, females appear to be more responsive during stress. For example, female rats exhibited higher levels and larger changes in corticosterone than did males during a 30-minute restraint condition (Livezey et al., 1985). Other studies have indicated that while females were less affected by a single two-hour restraint than were males, they showed greater long-term effects of repeated restraint and did not appear to adapt as readily (Kennet et al., 1986). Evidence from a study using a corticosterone synthesis inhibitor (metyrapone) indicated that corticosterone increases during restraint contributed to female rat's failure to adapt (Haleem et al., 1988). When production of corticosterone was blocked, female rats showed the same long-term adaptation as did males, suggesting that the relative hypercorticosteronemia exhibited by females played a role in their adaptation difficulties. In another study, female rats exposed to restraint, forced running or shock, exhibited more rapid increases in corticosterone after exposure to a stressor (Kant et al., 1983).

The reason(s) for sex differences in responses to stressors are not clear, and factors operating at any one of several levels could be responsible. Men and women

could differ in how events are perceived or interpreted, in how they cope with these events or perceived pressures, or in constitutional mediation of the stress responses. Any of these possibilities could influence fundamental physiological and pathophysiological processes. The present studies examined the latter possibility, that some of this variation may be physiologically mediated by differential responsiveness of organs or systems involved in the stress response. Specifically, differential sensitivity of the pituitary to hypothalamic stimulation and of the adrenal cortex to hypophyseal discharge were evaluated among men and women. Hence, we compared the functional integrity of the pituitary and adrenal components of this axis in men and women by examining responses to pharmacologic provocation of the stress response with little or no perceptual or behavioral mediation. In a first set of studies, ACTH and cortisol responses to exogenous ovine corticotropin-releasing hormone were studied. In a second set, cortisol responses to infusions of synthetic ACTH were examined. By utilizing these two techniques, we were able to compare the responsiveness of the HPA axis in men and women at the pituitary and adrenal levels, respectively.

Methods

Study I

Subjects

A total of 43 healthy volunteer subjects (24 men and 19 women) participated in this study. The mean ages for men (29.3 ± 5.1 s.e. years) and women (27.3 ± 5.7 s.e. years), were comparable and all subjects were screened and examined by medical staff and showed no evidence of cardiac, pulmonary, hematologic, hepatic, renal, endocrine, neurologic, or psychiatric illness. All subjects were studied at the Clinical Center of the National Institutes of Health. Menstrual cycle phase was not assessed but previous studies have found no differences in plasma ACTH responses to CRH or in cortisol responses to hormonal stimulation across different phases of the menstrual cycle (Rabin, in press; Rittmaster, personal communication). Testing with CRH was performed after obtaining informed consent and demographic information from each subject.

CRH Stimulation Test

Ovine corticotropin-releasing hormone was obtained from Bachem (Torrance, Calif), prepared as previously

described (Chrousos et al., 1984; Gold et al., 1988) and administered as an intravenous bolus injection at 8 p.m., when the hypothalamic-pituitary-adrenal axis is normally quiescent. A dose of 1.0 ug/Kg was selected because prior studies with primates (including humans) suggested that this was the lowest dose at which maximal stimulation of cortisol is achieved (Orth et al., 1983; Schulte et al., 1984).

Material and Methods

An intravenous catheter was inserted into the antecubital vein approximately one hour before the start of the study and the IV line was kept open with 100 U/ml sodium heparin. The subjects were asked to relax during the test sitting quietly and reading if they chose to do so. Blood samples were drawn 15 minutes before the administration of CRH, at the time of the injection, and 5, 15, 30, 60, 90, and 120 minutes after administration of CRH for measurement of plasma ACTH and cortisol. Blood was collected in pre-chilled glass tubes containing EDTA. The samples were immediately placed on ice and the plasma was separated and stored at -20 C until assay. Plasma ACTH and cortisol were measured by radioimmunoassay (RIA) (Chrousos et al., 1984). Dose interpolations for the

radioimmunoassay were performed with the use of computer-assisted logit-log analysis.

Data Analysis

The pituitary and adrenal responses to CRH stimulation were first analyzed as raw scores, using a two-way repeated measure analysis of variance with time as the repeated measure. In addition, these responses were integrated over time and expressed as area under the response curve from 0 to 120 minutes. The net integrated area was expressed as the area beneath the response curve from 0 to 120 minutes minus the area corresponding to the mean of the two baseline values times 120 minutes. Peak ACTH and cortisol values were also considered corresponding to the highest values achieved during the test, which occurred during the first hour after the administration of the hormone.

Study II

In order to determine whether men and women exhibit differential sensitivity to varying doses of ACTH, male

and female subjects underwent five ACTH stimulation tests at varying dose levels. If no differences in sensitivity appeared, it would suggest that higher levels of cortisol during or after stress are more likely mediated at the pituitary rather than the adrenal cortex. Differences in either direction would have implications for interpreting the data from Study I.

Subjects

Five healthy men and five healthy women participated in this study. Mean ages for these subjects were comparable ($X_m = 29.4$, $X_f = 34.0$) and subjects were screened by medical staff and judged free from illness and psychopathology. Subjects were studied at the Clinical Center of the National Institutes of Health, and were excluded if they showed evidence of renal, hepatic, or thyroid disturbances. Testing was performed after obtaining informed consent from each subject.

ACTH Stimulation Test

Men and women underwent a series of five one-hour ACTH tests, performed at a minimum of three days apart.

In a randomized, blinded fashion, one of five different doses of synthetic ACTH₁₋₂₄ (Cortrosyn: 0, 0.003, 0.01, 0.1, and 2 mg/kg) was administered intravenously at 7:00 p.m. Blood was drawn through an indwelling catheter at 0, 10, 30, and 60 minutes relative to the intravenous bolus of ACTH₁₋₂₄ for measurement of plasma cortisol. Cortisol determinations were made by RIA's as described in the methods section. Peak values of cortisol represent the highest value obtained after ACTH₁₋₂₄ administration. Change in cortisol responses were indexed by subtracting the basal (i.e., 0 mg/kg dose) from the peak values. Total-integrated plasma cortisol values represent the total area beneath the time-integrated curves from 0 to 60 minutes following ACTH₁₋₂₄ administration. Net integrated values were determined by subtracting the product of the basal level times 60 minutes from the total-integrated value.

Results

The results from study 1 indicate that there were no significant sex differences in basal plasma ACTH or cortisol, but a main effect of sex-of-subject indicated that women had higher levels of ACTH across the session than did men, $F(1,41) = 4.5, p < .04$. This was qualified by a main effect of time as ACTH levels increased over the session, $F(1,41) = 85.2, p < .001$. The interaction of time and sex was also significant, indicating that ACTH levels were similar before the injection of CRH but that they diverged markedly afterward, $F(7,47) = 6.0, p < .001$. Women exhibited higher levels of ACTH at each sampling following CRH administration (see Figure 1). Cortisol data did not yield a main effect of gender but showed a significant increase over time, $F(1,41) = 180.2, p < .001$. An interaction between the sex-of-subject and time variables indicated that men and women had similar cortisol levels prior to CRH administration but that women eventually exhibited higher levels more than an hour later $F(6,41) = 3.8, p < .01$ (see Figure 2).

In addition, compared with males, female subjects also had higher peak ACTH responses ($X_m = 23.1, x_f = 33.9$), $t(41) = 2.9, p < .01$), greater total ACTH responses

($X_m = 2060.4$, $x_f = 2791.2$), $t(41) = 2.4$, $p < .05$), and greater net ACTH responses ($X_m = 1178.2$, $x_f = 2041.6$), $t(41) = 3.2$, $p < .01$). Despite these relative elevations in ACTH secretion, women's plasma cortisol responses were generally not significantly different from those of men; peak cortisol levels, total cortisol response and basal cortisol levels were not significantly different for men and women. Only net cortisol, reflecting magnitude of change from baseline over time, approached significance ($X_m = 11101.9$, $x_f = 1365.9$), $t(41) = 1.9$, $p < .07$.

In study 2, an analysis of variance comparing men and women across the five ACTH dose levels (repeated measure) indicated that there was a significant effect of dose; all subjects showed increases in peak cortisol levels as ACTH dose increased, $F(4,38) = 36.8$, $p < .001$. Dose also affected the magnitude of change in cortisol levels; the larger the dose of ACTH, the larger the changes in cortisol level over the one-hour session, $F(4,38) = 31.8$, $p < .001$. However, no significant effects of sex-of-subject or interactions between this variable and dose were observed. Additionally, there were no significant differences between men and women in change, total, or net cortisol levels.

DISCUSSION

Our first study considered the possibility that women respond to stress or challenge with larger ACTH and, hence, cortisol responses than men. CRH is secreted by the hypothalamus during stress, stimulating the pituitary gland to release adrenocorticotropin hormone and that in turn stimulates the adrenal gland to release cortisol. By comparing these HPA responses to a bolus injection of CRH between men and women, we were able to observe differences in sensitivity of the pituitary corticotroph to CRH. Women were more responsive to CRH stimulation, attaining significantly higher levels of ACTH than men over a two-hour post-CRH period. Peak plasma free cortisol levels at 60 minutes following CRH administration were significantly elevated in women compared to men, concomitant with their relatively increased plasma ACTH response to CRH. We also observed significantly higher total plasma cortisol levels in women confined to the 90 and 120 minute post-CRH time points, at which time plasma cortisol levels were falling in both groups. However, differences in cortisol secretion were not as striking, leading to speculation that biological differences in HPA axis sensitivity between men and women lie primarily in the pituitary or higher centers. Whether these differences also

characterize adrenal response to ACTH is less clear from these data and was studied in our second experiment. The data from our second study indicate a similar dose response relationship of plasma cortisol levels to ACTH administration in men and women, and suggest that the sensitivity of the adrenal cortex to ACTH is quite similar in both sexes.

These data are compatible with a relative enhancement in pituitary corticotroph sensitivity to CRH in women compared to men. As basal, total and free plasma cortisol levels did not significantly differ between men and women, this finding does not appear to be a consequence of differences in the central set point for cortisol secretion. However, we cannot definitely rule out the possibility of sex differences in 24-hour urine free cortisol, which was not measured in this study, not reflected at 2000h, when plasma cortisol levels tend to be minimal. Alternatively, these data could be explained by relative insensitivity of the pituitary corticotroph to glucocorticoid negative feedback in women as compared to men. However, such an insensitivity would have to be localized to the pituitary gland, since if present at the hypothalamic level, one would expect basal cortisol levels to be elevated. As yet, little is known regarding site-specific regulation of glucocorticoid receptors.

These data could be explained due to chronically enhanced CRH priming of the pituitary corticotroph by some factor which is secreted in different amounts in women and men. Although several such factors are possible candidates, estrogens and/or vasopressin seem most likely to be involved. Hence, estrogens have been shown to modulate the hormonal response to stress at the pituitary, (Peiffer and Barden 1989), and at the hypothalamus, (Turner and Ansari, 1989), by controlling the synthesis of glucocorticoid receptors. The possibility of a relative glucocorticoid resistance in women at either the hypothalamus or pituitary is consistent with data indicating that progesterone functions as a weak glucocorticoid antagonist, and would suggest that for a given cortisol level, women would have to secrete more CRH than men. In this regard, the CRH mediated hypercortisolism in psychiatric states, such as major depression and anorexia nervosa, are much more common in women than men. It should be noted however, that Rabin et al, 1991, have shown that there are no differences in ACTH and cortisol responsiveness to CRH between the two phases of the menstrual cycle, in normal women. In addition, the hypercortisolism in depressed patients does not seem to reflect the presences of glucocorticoid resistance (Kling et al, 1989).

Another possibility for the enhanced ACTH response to CRH in women is that women secrete more arginine vasopressin (AVP) into the hypophyseal portal blood and/or peripheral plasma than men. In this regard, AVP and to a lesser extent Oxytocin (Gibbs, 1986) is believed to be a strong positive modulator of the pituitary ACTH response to CRH. If this latter finding were also true in humans, then higher vasopressin levels could contribute to the enhanced responsiveness of the corticotroph in female subjects to the exogenous administration of CRH. Moreover, because AVP-induced ACTH secretion appears to be more resistant to negative feedback effects of glucocorticoids than that stimulated by CRH alone, (Bilezikjian et al, 1987), even a subtle hypersecretion of AVP by women could result in insufficient amplification of CRH-induced ACTH secretion to account for the differences observed in this study. This may be of some significance in light of recent studies reporting that the hypothalamic paraventricular nucleus contains functionally different CRH-containing components, including one containing CRH alone which may mediate the basal rhythm of circulating glucocorticoids, and another containing both CRH and AVP which may specifically mediate ACTH responses during acute stress (Whitnall, 1989).

The hyperresponse of ACTH to CRH in normal women is interesting, given the fact that several states associated

with hypercortisolism, depression, anorexia nervosa and Cushing's disease, are more prevalent among women than men. Studies have indicated that, compared to controls, depressed and anorexic patients showed blunted ACTH responses to exogenous CRH in association with basal hypercortisolism (Gold et al, 1988). Patients with Cushing's disease on the other hand, showed an exaggerated response. Because these illnesses are more common among women, it is possible that differences in the sex ratios in control and patient population could have contributed to these findings. Future studies of pituitary-adrenal responses to CRH should be carefully sex-matched in order not to introduce bias. Similarly, future studies using CRH to evaluate the functional integrity of the pituitary corticotroph cell in human subjects should take into account these male to female differences.

In summary, the present study adds to a growing body of literature regarding sexual dimorphism in a variety of behavioral and physiological parameters in humans. Whether this male female difference in the responsiveness of plasma ACTH secretion to CRH administration has behavioral or physiological consequences remains to be determined.

Figure Captions

- Figure 1: Plasma ACTH response to CRH in normal men and women (mean \pm SEM, * P < .05).
- Figure 2: Plasma cortisol responses to CRH in normal men and women (mean \pm SEM, * P < .05).
- Figure 3: Plasma cortisol responses to ACTH in normal men and women (mean \pm SEM).

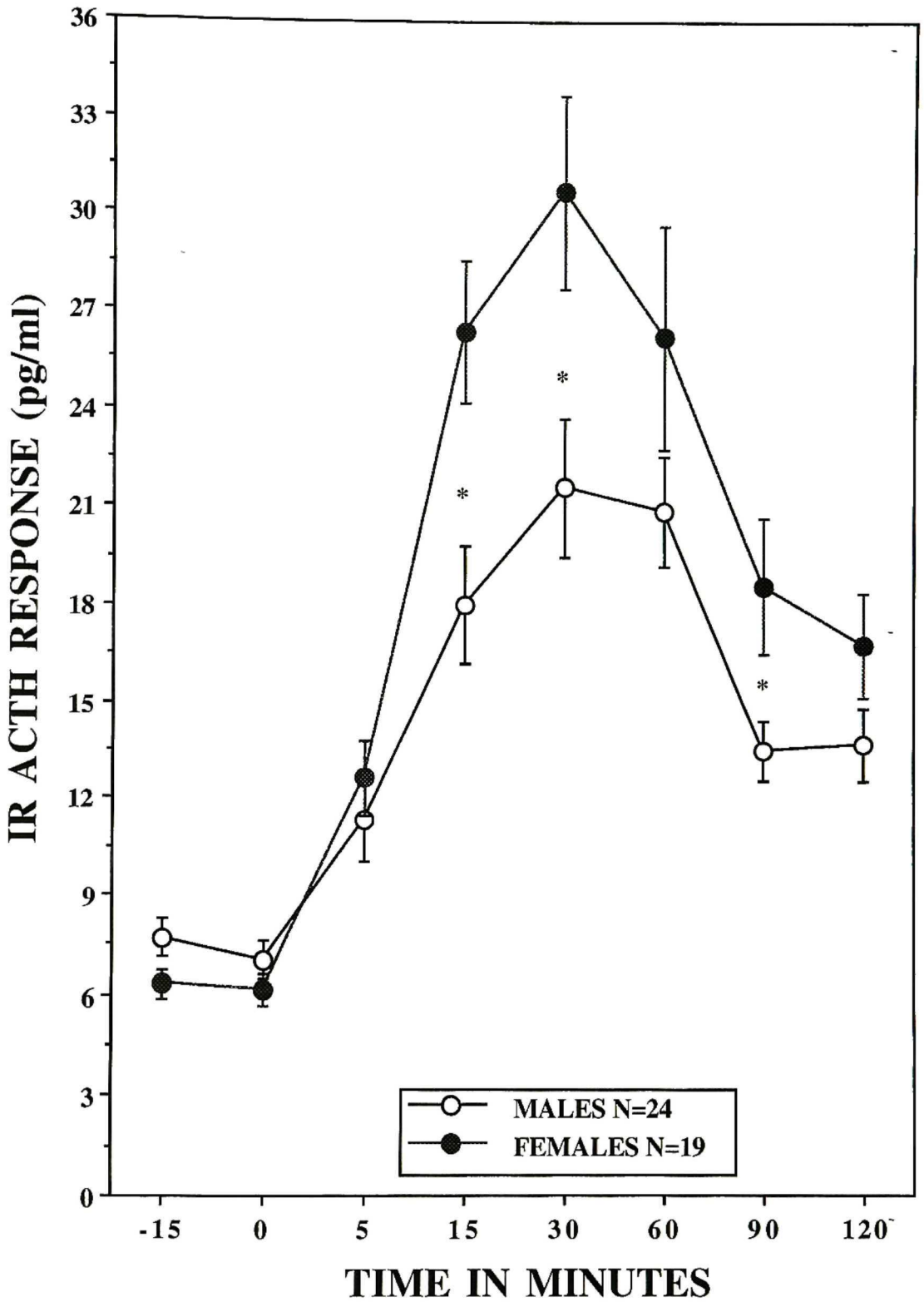


Figure 1. Plasma ACTH responses to CRH in normal men and women. Mean \pm SEM are shown. * $P < 0.05$ ANOVA

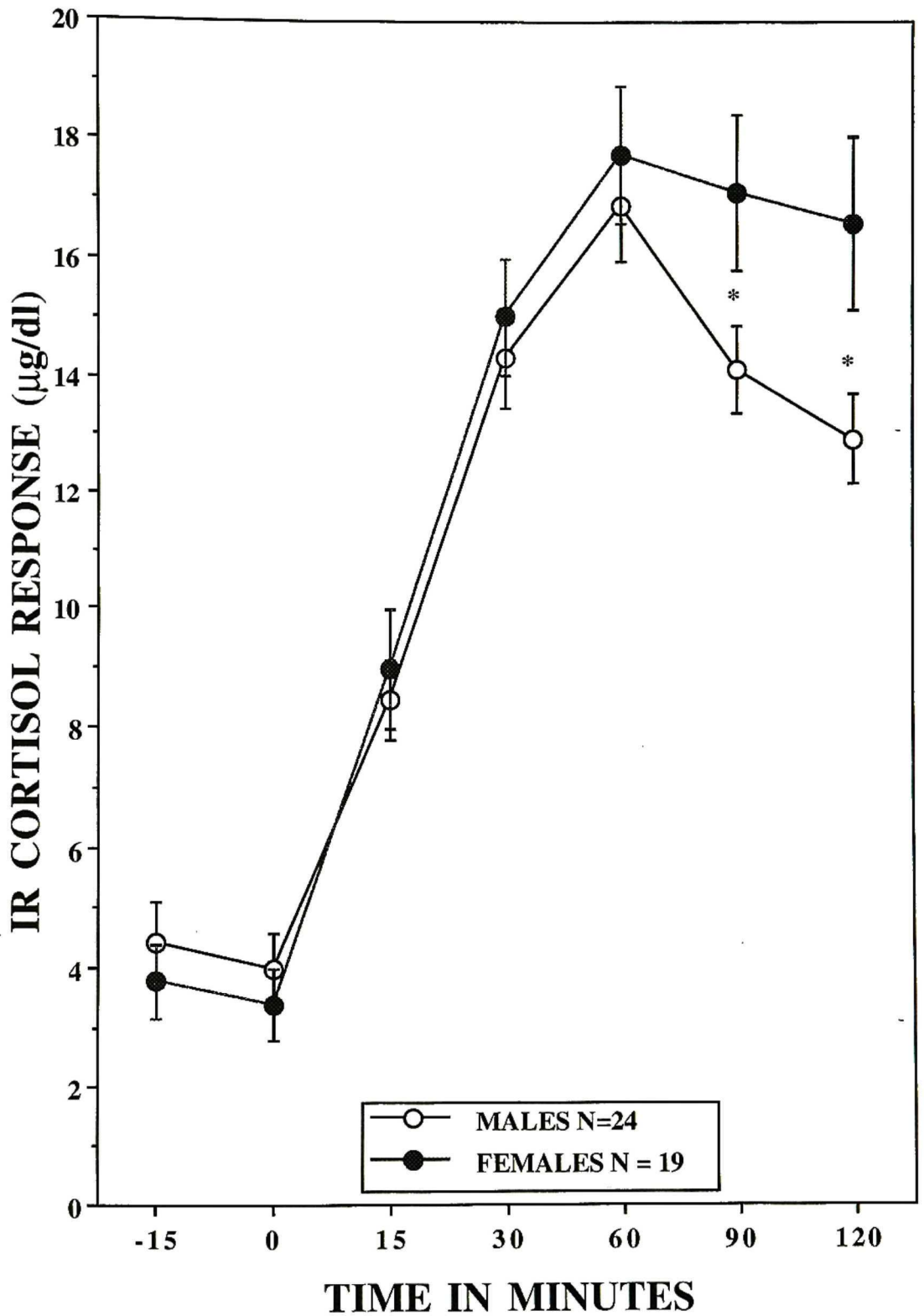


Figure 2. Plasma cortisol responses to CRH in normal men and women. Mean \pm SEM are shown. * $P < 0.05$ ANOVA

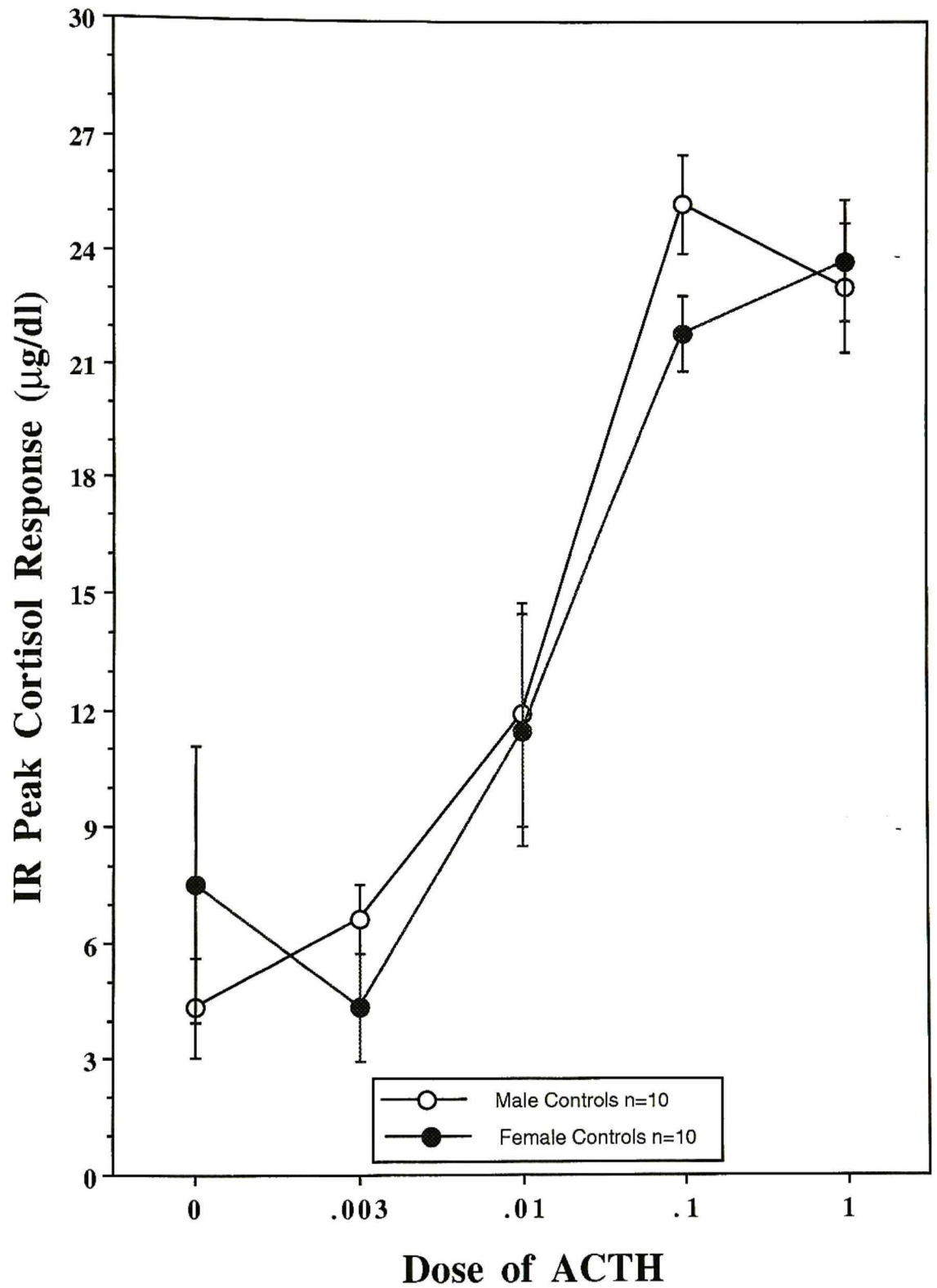


Figure 3: Dose response curve for ACTH administration at Five different doses

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