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Age-Dependent and Gender-Dependent Regulation of Hypothalamic-Adrenocorticotropic-Adrenal Axis

Johannes D. Veldhuis, MD[a,*], **Animesh Sharma, MBBS**[a], and **Ferdinand Roelfsema, MD, PhD**[b]

[a]Endocrine Research Unit, Mayo School of Graduate Medical Education, Center for Translational Science Activities, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA [b]Department of Endocrinology and Metabolic Diseases, Leiden University Medical Center, Albinusdreef 2, Leiden 2333ZA, The Netherlands

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OVERVIEW OF REGULATED GLUCOCORTICOID PRODUCTION

Clinical observations indicate that diverse disorders disrupt hypothalamic-corticotropic-adrenal (HPA) homeostasis. Prominent examples include depression, mania, dementia, posttraumatic stress disorder, chronic fatigue syndrome, alcoholism, visceral adiposity, diabetes mellitus, polycystic ovarian disease, acute illness, systemic disease, and multiorgan failure.[1–19] Age, gender, and sex steroids are salient physiologic factors that determine the magnitude and duration of stress-adaptive cortisol production, albeit via mechanisms that are essentially unknown in the human.[20–34]

Understanding the regulation of normal HPA outflow is significant, because chronically increased glucocorticoid concentrations correlate with metabolic features of syndrome X (visceral adiposity, insulin resistance, low high-density lipoprotein levels, high blood pressure, increased triglyceride levels), physical frailty (reduced bone and muscle mass, decreased aerobic capacity), immune suppression, hypogonadism, growth hormone (GH), and insulinlike growth factor 1 deficiency and impaired memory and spatial cognition (Fig. 1).[15,35–44] Aging itself is associated with similar changes (Box 1). Accordingly, there is an ongoing scientific need to elucidate the basic mechanisms that govern cortisol homeostasis in the aging human.[22,26,27,32,45–51] Inferable effects of aging on HPA function may be confounded by multiple factors, including gender, stress, and genetics (Box 2).

DIURNAL ADRENOCORTICOTROPIC HORMONE AND CORTISOL RHYTHMS

In principle, age could modulate mean hormone concentrations, secretion rates, elimination kinetics, pulse size (amplitude) or number (frequency), pattern regularity, or circadian (approximately 24-hour) rhythms. Nycthemeral (night-day) cortisol rhythms are consistently

*Corresponding author. veldhuis.johannes@mayo.edu.

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altered in aging individuals (Box 3). Most clinical studies report a phase-advanced acrophase (clock time of maximal adrenocorticotropic hormone (ACTH) or cortisol concentrations within the 24-hour day), eg, 06:30 AM (older) vis-à-vis 09:00 AM (young). Concomitantly, there is an increased circadian nadir (lowest 24-hour concentration) in the late evening and through midnight.[52–54] The higher nadir blunts the overall 24-hour increase in cortisol levels. Possible relevance of these findings is that certain target-tissue effects of cortisol, such as reduced lymphocyte subtype populations, share in the phase shift.[55,56]

Sleep disruption (reduced deep sleep or early awakening) occurs in many older people.[57–59] The degree to which these alterations reflect or cause aging-associated changes in functional disability, anxiety, depression, social support, caloric intake, and lifestyle modifications is not clear.[60–65] However, structural alterations in the hippocampus, suprachiasmatic nuclei, hypothalamus, adrenal gland, and possibly the autonomic nervous system can accompany aging in animals (Box 4).[66–68] A confounding unresolved issue is the extent to which memory or cognitive decline in older adults results from (is caused by) versus elicits (causes) increased cortisol secretion in the late day.[69–71] Available data do not exclude bidirectional effects.[72–74]

HPA ALTERATIONS IN AGED ANIMALS

Significant functional changes occur in the HPA axis of aged laboratory animals (Box 5). A consistent adaptation is reduction in brain corticosteroid receptors, type I (MR) and type II (GR).[75] Both mRNA and protein levels of MR and GR decline in the aged male Fischer rat. This model shows increased hypothalamopituitary portal venous CRH, consistent with a functional decrement in corticosteroid negative feedback. However, species and strain differences limit the consistency of laboratory animal models.

EXPERIMENTAL INSIGHTS INTO AND CLINICAL INFERENCES REGARDING SEX-STEROID REGULATION OF GLUCOCORTICOID AVAILABILITY

Experimental Insights

Sex steroids direct key regulatory mechanisms within the HPA axis of several mammalian species (ie, rat,[76–84] mouse,[85] sheep,[86,87] monkey[88,89] and human[46,90–92]). How gonadal steroids regulate ACTH and cortisol secretion is well articulated in the young adult rat, as highlighted in Fig. 2. Sex differences in HPA regulation in the rodent arise from both neuronal imprinting during early development and distinct actions of estradiol (E_2) and testosterone (Te) in adulthood.[93–97] In the young adult animal, exposure to E_2 typically potentiates stress-induced ACTH secretion by: (1) attenuating negative feedback in the hypothalamus, hippocampus, amygdala, and pituitary gland[98,99]; (2) inducing AVP, CRH, and CRH-R1 gene expression in the paraventricular nucleus (PVN)[77,93,100–103]; (3) enhancing adrenal responsiveness to ACTH[104–107]; (4) muting hippocampal and bed nucleus of the stria terminalis–directed inhibition of PVN neurons[108]; and (5) blunting homologous downregulation of limbic GR.[76] Conversely, Te and 5α-dihydrotestosterone (5α-DHT) generally exert opposing effects on the fore-going mechanisms, resulting in diminished stress-stimulated ACTH secretion (see Fig. 2).[6,81,84,109–114] What remains unclear is how aging per se modulates the sex-steroid effects.

The impact of gonadal steroids in the rat is not expressly dichotomous, because E_2 may augment certain actions of 5α-DHT, whereas 5α-DHT can impede other effects of E_2[115–117]. In addition, in some studies, low concentrations of estrogen diminish rather than amplify stress-induced ACTH and glucocorticoid secretion in the ovariprival state.[82,118,119]

Clinical Inferences

Certain HPA modulators and stressors affect ACTH and cortisol homeostasis, with strong age dependence and female or male predominance (Box 6).[21,22,46,120–122] Modulators in this category include CRH, AVP, DEX, somatostatin, social stress, cognitive stress, and pharmacologic probes. Most often, greater responses occur in aging, especially in women. The precise bases for age-associated gender selectively in these clinical settings is not established. Investigations in the human are limited in scope and discrepant in inference. Critical review shows the following fragmentary and disparate observations:

- **a.** Daily cortisol secretion rates are higher in men,[123,124] greater in older women,[125] comparable in women and men,[126–130] and increased in young women in the luteal compared with follicular phase of the menstrual cycle[131,132];
- **b.** Maximal ACTH-stimulated cortisol secretion is greater in women,[33,49,133] similar by gender,[126] accentuated by Te administration in women,[134] or unaffected by estrogen in men[31,34,135];
- **c.** Maximal CRH-stimulated ACTH or cortisol secretion is equivalent in the 2 sexes,[26,27,46] higher in men,[136] greater in women,[32,42,48,136–139] not affected by E_2 in women,[140] in augmented by E_2 in men[141] or suppressed by Te men[142];
- **d.** AVP-induced ACTH secretion is comparable in the 2 genders[47] or greater in women[48];
- **e.** Synergy between CRH and AVP is greater in men than women or comparable by gender[46];
- **f.** Stress-induced elevations in ACTH and cortisol concentrations are greater in men,[22,23,25,143–146] greater in women,[28,145,147] comparable by gender,[26,32] repressed by E_2 in women, and dependent on age[22,25,26,28,122,144] or independent of age[32];
- **g.** Delayed (integral) glucocorticoid negative feedback is either muted in women[32,48,148] or accentuated in women[148,149] compared with men;
- **h.** Rapid cortisol-mediated negative feedback has been studied in men,[149] but responses have not been compared in women and men; and i. The metabolic clearance rate of cortisol is the same in the 2 sexes,[126,130] decreased in women[150] or increased in women.[91]

The foregoing inconsistencies and the lack of precise data on body compositional effects preclude definitive inferences regarding putatively joint interactions among age, gender, sex steroids and body-fat distribution in regulating glucocorticoid availability in humans.

Glucocorticoid Negative Feedback Studies in the Human: Confounding by Gender and Age

Increased glucocorticoid concentrations and impaired suppression of ACTH and cortisol concentration by DEX tend to correlate with increased age and decreased cognitive function.[15,38,151,152] Although such observations could signify that aging increases mean cortisol levels and reduces glucocorticoid negative feedback, clinical data are controversial. For example, awakening morning salivary cortisol seems to decrease with age, especially in women (Box 7). In contrast, cortisol responses to glucose less than 50 mg/dL are preserved in aging.[153] In 1 study, feedback inhibition of ACTH and cortisol concentrations by graded doses of DEX did not differ in older and young men.[29] In other investigations, intravenous (IV) infusion of cortisol suppressed ACTH concentrations less in older than young men, and more in postmenopausal women than elderly men.[149,154,155] Analogously, DEX administration lowered cortisol concentrations more in 106 women than 203 men aged 66 to

78 years.[156] Assessments of rapid negative feedback have typically used pharmacologic doses of cortisol (5–50 mg IV) without evaluating age and gender effects.[149,157,158] Experimental data indicate that feedback effects and loci of inhibition differ between synthetic glucocorticoids and cortisol.[159] Box 7 presents several other age (and gender) effects on human HPA dynamics, showing variously no effect, diminution, and accentuation of ACTH/cortisol responses to distinct stressors in aging humans. Age does not seem to alter responses to infusions of insulin, naloxone, or ACTH. Aging attenuates ACTH/cortisol responses to speech stress, low socioeconomic status, deep sleep, psychosocial stress, and MR stimulation with 9α-fludrocortisone, and potentiating HPA responses to an MR antagonist and a selective serotonin uptake inhibitor.

UNRESOLVED ISSUES

Delineating Relevant in Vivo Cortisol Feedback Signals

Free (protein-unbound), cortisol-binding globulin (CBG), and albumin-bound cortisol concentrations constitute respectively 6%, 80%, and 14% of total plasma cortisol in the human.[126,160] Indirect evidence points to greater biological relevance of free than total glucocorticoid concentration in mediating certain tissue-specific effects, such as hippocampal GR occupancy, negative feedback efficacy, stimulation of glycogen synthesis, fractional hepatic extraction, and uptake into cerebrospinal fluid.[161–164] Clinical studies are needed to quantify negative feedback control of CRH and AVP secretion and stimulation of ACTH secretion by each of free, CBG-bound, and albumin-bound cortisol in young and older women and men exposed to E_2, Te, and GR or MR antagonists.

Estimating Condition-Specific and Subject-Specific Kinetics of Cortisol and ACTH Elimination

In the human, the nominal half-life of total cortisol is 35 to 65 minutes.[126,127,165,166] Longer half-lives occur with higher CBG concentrations in estrogen-rich young women than Te-predominant men.[167,168] Model-based analyses of the fate of cortisol in plasma in middle-aged adults predict gender-independent half-lives of free cortisol diffusion of 1.8 minutes and of free and total cortisol elimination of 4.1 minutes and 48 minutes, respectively.[126] Such calculations also forecast higher free and albumin-bound cortisol concentrations in the morning than evening and thereby more rapid clearance, as observed clinically.[169] The half-life of human ACTH is reportedly 8 to 25 minutes by bioassay and immunoassay.[126,165,170,171] Rapid ACTH disappearance imposes a requirement for frequent blood sampling to monitor pulsatile secretion.[172–174]

Noninvasive Analyses of Multisignal Regulation of ACTH Secretion

New analytical procedures are needed to reconstruct feedforward and feedback dose-response properties using only paired measurements of linked hormones. The objective is to obviate the previous long-standing necessity to inject agonists, antagonists, or marked molecules.[126,175,176] Implementation of 1 such methodology in 32 healthy adults ages 26 to 79 years permitted estimation of unstressed ACTH feed-forward efficacy (maximal cortisol secretion), potency (one-half maximally effective concentration, [EC_{50}]) and adrenal sensitivity (absolute slope of effector-response relationship).[126] A computed EC_{50} (potency) of endogenous ACTH of 24 ± 3.3 ng/L was associated with a mean plasma ACTH concentration in the same cohort of 19 ± 6.2 ng/L. Empirical validation of the equation set was by frequent (5-minute), extended (4-hour–12-hour) direct sampling of hypothalamopituitary portal and internal-jugular blood to measure CRH, AVP, ACTH, and cortisol as well as gonadotropin-releasing hormone, luteinizing hormone, and Te concentration in the awake unrestrained horse and sheep.[175,176] Statistical verification was by direct mathematical proof of maximum-likelihood estimation of all parameter

asymptotes.[176] An extension of this concept is to reconstruct the 3-parameter relationship among CRH concentration, AVP concentration, and ACTH secretion at a given steady-state cortisol concentration using data from pituitary portal vessels (Fig. 3).[177] Based on these methods, estimated ACTH efficacy decreases in men and increases in women with age (Fig. 4).[178] In addition, age and body mass index together determine adrenal sensitivity to endogenous ACTH (Fig. 5).

Other Diurnal Rhythms in Aging

Melatonin, core body temperature, DHEA, T-helper cells, slow-wave sleep, and other nycthemeral rhythms are also flattened with age (Box 8). The relationship between these and HPA changes is not known. GH secretagogues also drive ACTH/cortisol secretion, but the mechanism is not defined.[179]

SUMMARY

Age, gender, and sex steroids represent key modulators of physiologically incremental and pathologically overt adaptations in the ensemble regulation of CRH, AVP, ACTH, and cortisol output.[126,165,175,180,181] Challenges in this arena include development and application of new safe rational approaches to identify, prevent, and treat deficient or excessive cortisol production. Further clinical investigations should aid in clarifying mechanistic HPA changes in aging and comorbid states (eg, increased visceral adiposity), with the goal of obviating HPA-associated morbidity, mortality, disability, and impaired quality of life in aging women and men.[181–183]

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Box 1

Similar changes occur in aging as in HPA hyperactivity

↓ physical performance if ↑ evening cortisol

↓ walking speed

↓ bone-mineral density in postmenopausal women

↑ functional disabilities

↓ immune responses

↑ syndrome X (visceral adiposity, ↑ blood pressure, ↓ insulin action)

↓ cognitive function ↓ memory

↑ depression

↑ blood pressure

↓ lean muscle mass

↑ insulin resistance ↓ glucose tolerance

Abbreviations: ↑, increase; ↓, decrease.

Box 2

Confounding factors in HPA evaluation with age

- Gender differences[90]
- Sex-steroid milieu[184]
- Cumulative glucocorticoid exposure[185]
- Dementia or depression[186]
- Genetic polymorphisms in HPA genes[187]
- Inflammation, obesity, weight loss, medication use, illness[130,188]
- Type of stress (psychosocial, physical, metabolic, cognitive)[189]
- Onset versus recovery of stress response[190]
- Structural brain changes[191]
- Cigarette smoking[63]
- Impaired sleep[192]
- Socioeconomic insecurity[63]
- Ethnicity, psychological traits[193]
- ↑, ↓ or unchanged serum total cortisol (ages 19–89 years)[125,130,194–198]
- ↓ urinary free cortisol in centenarians[65]
- ↓ circannual free cortisol rhythm[197]

Box 3

Circadian cortisol changes with age

- Late-day and evening increases in cortisol levels[54,63,125,199]
- Earlier morning cortisol maximum (phase advance)[68,125,195,200,201]
- Lower circadian amplitude (24-hour decrement for peak minus nadir)[54]
- More irregular (less orderly) cortisol secretion patterns[200]

Box 4

Age modifies selective components of HPA axis in animals and humans

Component of Axis	Age Effect
Hippocampus	↓ GR and ↓ MR
Suprachiasmatic nucleus (circadian)	↓ VIP (older men only)[202]
Hypothalamus (paraventricular nucleus)	↑ CRH ↑ AVP[a,203]
Pituitary gland	No change in ACTH
Adrenal gland zona reticularis	↓ DHEA[a,204,205]
Autonomic nervous system	↓ NE outflow[a]
Plasma cortisol-binding globulin	No change[a,130]
Monocytes	↓ GR (both sexes)[206]

Abbreviations: AVP, arginine vasopressin (ADH); DHEA, dehydroepiandrosterone; GR, glucocorticoid receptor; MR, mineralocorticoid receptor; NE, norepinephrine; VIP, vasoactive intestinal polypeptide.

[a]Human data.

Box 5

Aged animals: HPA alterations

↓ hippocampal MR and GR in Fischer-344 rat[207]

↑ portal venous CRH (Fischer)[208]

↓ portal venous AVP (Fischer)[208]

↑ corticosterone (Long-Evans rat)[209,210]

↓ hippocampal MR but not GR[209]

↑ evening cortisol (female Rhesus monkey)[211]

↓ cortisol escape after dexamethasone (DEX)[211]

Box 6

Gender-related and age-related distinctions in human HPA responsiveness

↑ or unchanged plasma ACTH with age[212–214]

↑ stimulation of CRH of ACTH and cortisol secretion[a,48]

↑ AVP/CRH (combined) stimulation[a,46]

↓ glucocorticoid suppression of effect of basal ACTH and CRH[48,56,74,148,149,213,215]

↑ paradoxic ACTH/cortisol response to somatostatin[216]

↑ social stress effect[a,22]

↑ response to cognitive stress[a,217]

↑ stimulation by 5HT-1A agonist (ipsapirone)[a,218]

↑ response to hypothermic stress[218]

↑ effect of physostigmine[a,219]

↑ cortisol response to naltrexone (opiate blocker)[a,220]

↑ ACTH/cortisol response to MR blocker[221,222]

[a] More prominent age contrast in women than men.

Box 7

Age-related changes in human HPA dynamics

1. Various stressors
   a. Depression
      i. ↑ cortisol with age in both sexes[196]
      ii. ↑ post-DEX/CRH cortisol with age[223]
   b. Memory impairment
      i. ↑ basal and post-DEX cortisol in older women with (vs without) memory impairment[69]
   c. Awakening
      i. ↑ salivary cortisol after meal[224]
      ii. ↓ salivary cortisol in older (vs young) adults especially women[60,224–227]
      iii. Salivary cortisol predicts:
         1. executive function positively in older adults[228]
         2. working memory positively in older men and declarative memory negatively (both sexes)[229]
   d. Hypoglycemia
      i. Normal cortisol response to ↓ glucose of 50 mg/dL with age[153]
   e. Speech task
      i. ↓ (salivary) cortisol response in older men only[230]
   f. Socioeconomic status
      i. ↓ (salivary) cortisol with age in socioeconomically matched women only[227]
   g. Sleep
      i. ↓ deep sleep and amplitude of 24-hour cortisol rhythm with age (men)[58,192]
   h. Abdominal visceral adiposity in older women
      i. ↓ estimated ACTH efficacy[231]
   i. Psychosocial stress
      i. ↓ ACTH increment after DEX/CRH in older (vs young) men[22]
   j. Mineralocorticoid agonist (9a-fludrocortisone)
      i. ↓ ACTH/cortisol suppression in older (vs young) men[232]
   k. Mineralocorticoid antagonist (spironolactone)
      i. ↑ cortisol more in older (than young) adults[222]
2. Adrenal feedback
   a. Hydrocortisone-imposed negative feedback (25-mg IV bolus)
      i. ↓ ACTH suppression in older men[149]
   b. DEX (0.25–3 mg orally)
      i. ↓ ACTH/cortisol suppression in:
         1. older volunteers[48,233,234]
         2. and in luteal-phase women[235]
3. Pharmacologic interventions
   a. ACTH infusion
      i. No age effect on maximal cortisol response[234]
   b. Naloxone infusion (stimulus to ACTH/cortisol)
      i. No effect of age on cortisol response in men[236]
   c. Selective serotonin reuptake inhibitor (citalopram)

i. ↑ ACTH secretion with age in men[237]

4. Sex-steroid interactions

a. Short-term (2-week–8-week) E_2 treatment

i. ↓ cortisol hyperresponsiveness after DEX/CRH in older women treated with estrogen[32,118,238]

ii. Progesterone potentiates cortisol release to exercise[239–241]

iii. E_2 has no effect (vs hypogonadism) on exercise response in young women[240]

Box 8

Other diurnal rhythms affected in aging

↓ melatonin secretion at night[194,213]

↓ core body temperature rhythm[242]

↓ DHEA-sulfate levels[201]

↓ CD4 T-helper cell rhythm[243]

↓ δ (slow-wave) [and rapid-eye-movement] sleep[57,59]

↓ salivary amylase on awakening[62]

↓ free Te peak and phase advance (earlier)[201]

↓ thyrotropin (centenarians)[65]

↓ interleukin 6, interleukin 1β concentrations[59,244]

KEY POINTS

- • Aging increases adrenocorticotropic hormone (ACTH)/cortisol responses to corticotropin-releasing hormone (CRH) (especially in women) and to vasopressin/CRH (especially in men).
- • Estrogen treatment reduces hyperresponsiveness in postmenopausal women.
- • Age decreases glucocorticoid feedback (inhibition), leading to slow ACTH recovery after stress.
- • There is no age effect on corticosteroid-binding globulin.
- • Cortisol responses to hypoglycemia (insulin tolerance test) are preserved in aging.
- • How body composition interacts with age in hypothalamic-corticotropic-adrenal regulation is not known.

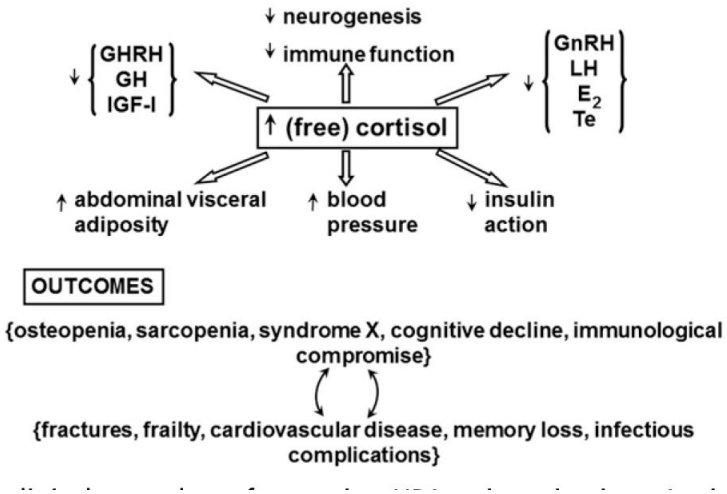

Fig. 1.

Putative clinical sequelae of excessive HPA axis activation. An increase in (free) cortisol availability is associated with adverse outcomes in diverse body systems.

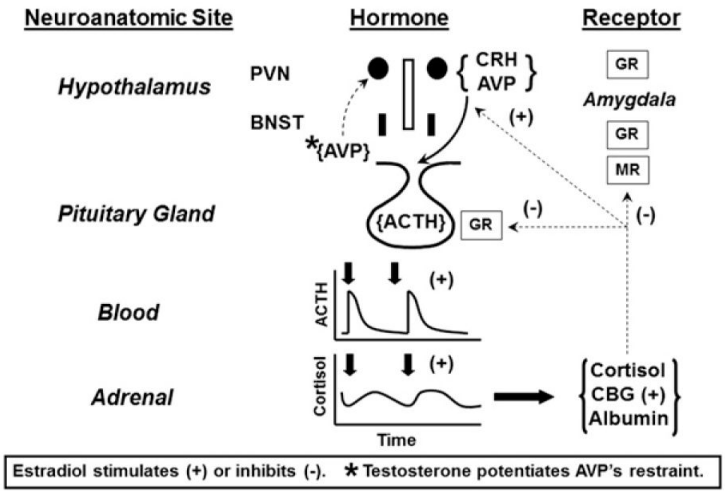

Fig. 2.

Experimentally based schema of loci of sex-steroid (estradiol and testosterone) control of HPA axis outflow. The + and − signs denote stimulation and inhibition, respectively.

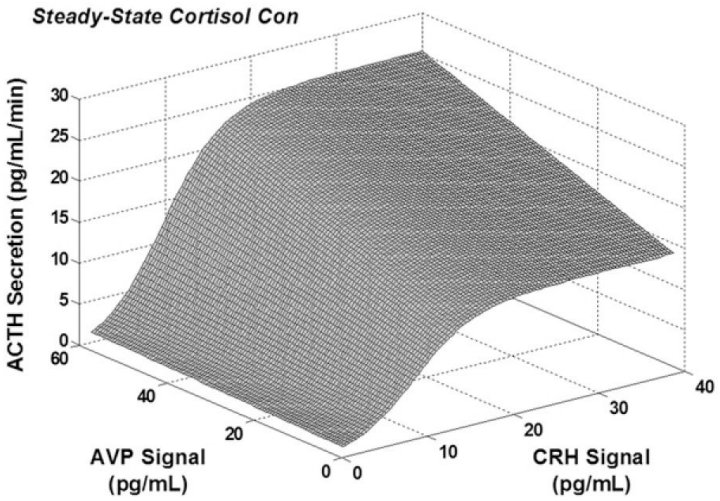

Fig. 3.

Joint AVP and CRH drive of ACTH secretion under fixed cortisol concentration (con) estimated from hypothalamopituitary portal venous sampling in the horse.

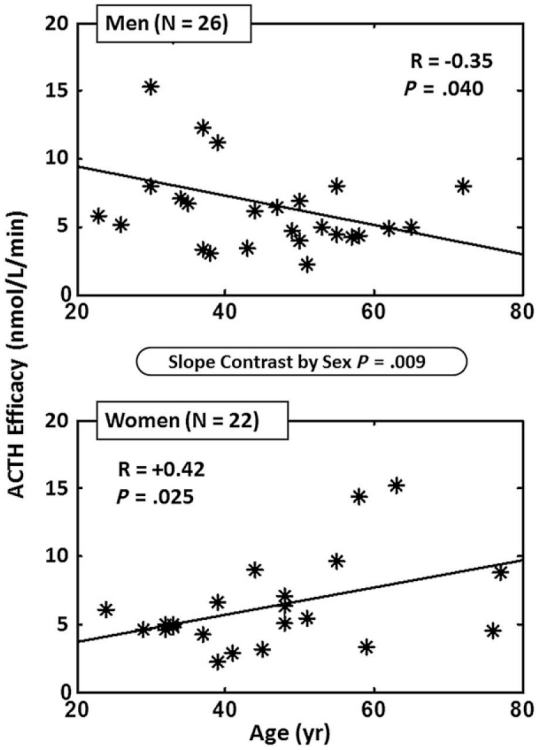

Fig. 4.

Opposite impact of age (independent variable) on ACTH efficacy (asymptotically maximal ACTH-stimulated pulsatile cortisol secretory rate) in men ($N = 26$, top) and women ($N = 22$, bottom). Pearson's product-moment correlation coefficients are shown for the regressions. The P value in the ellipse denotes the gender difference in slopes. (Adapted from Keenan DM, Roelfsema F, Carroll BJ, et al. Sex defines the age dependence of endogenous ACTH-cortisol dose responsiveness. Am J Physiol Regul Integr Comp Physiol 2009;297(2):R515–23; with permission.)

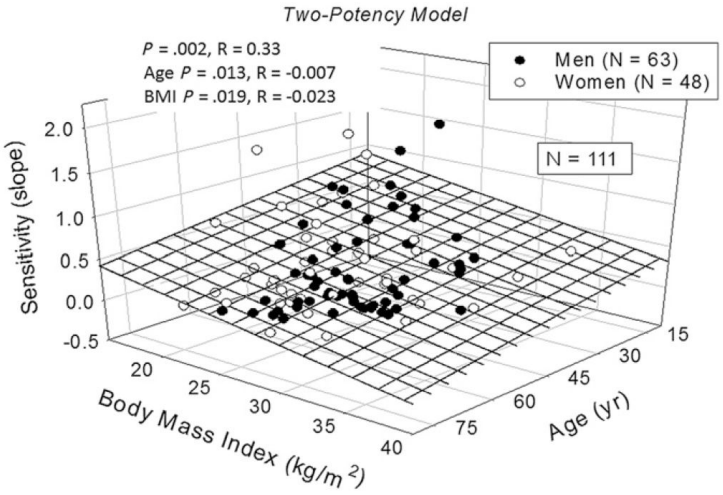

Fig. 5.

Age and body mass image (BMI) jointly attenuate adrenal sensitivity (maximal slope of ACTH-cortisol dose-response function) in a cohort of 111 healthy adults (overall $P = .0017$). Sensitivity was negatively associated with both age ($P = .014$) and BMI ($P = .019$), indicating reduced adrenal cortisol secretory responsiveness per unit increase in ACTH concentrations. R values are the correlation coefficients. (*Adapted from* Veldhuis JD, Iranmanesh A, Roelfsema F, et al. Tripartite control of dynamic ACTH-cortisol dose-responsiveness by age, body mass index and gender in 111 healthy adults. J Clin Endocrinol Metab 2011;96(9):2874–81; with permission.)