Gender determines ACTH recovery after experimental hypercortisolemia in older individuals

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Introduction

- Available clinical literature raises the possibility that stress-responsive mechanisms differ by gender, especially in older individuals
- In the rodent, female sex (and estradiol) and male sex (and testosterone) respectively potentiate and attenuate stress responses
- However, in human subjects, gender plays an equivocal role in regulating the hypothalamic-pituitary-adrenal (HPA) axis, possibly due to interactions between gender and age as well as gender and stressor type

Objective

- To determine the impact of gender in feedback inhibition and feedforward recovery of the hypothalamic-pituitary-adrenal (HPA) axis during and after an experimental cortisol infusion in older subjects

Methods

- We conducted a prospectively randomized double-blind, placebo-controlled, crossover study in 10 older men and 10 post-menopausal women
- During four separate hospital visits, each subject received oral placebo and intravenous saline (IVS), or oral ketoconazole (KTCZ) and an infusion of either IVS, low-dose (2.5mg/m^2) cortisol (LDC), or high-dose (10 mg/m^2) cortisol (HDC)
- ACTH and cortisol concentrations were measured every 10 minutes during the last 4 hours of the saline and cortisol infusions (feedback-clamp phase) and for 10 hours thereafter (recovery phase) **(Fig. 1)**

Results

- Gender did not determine mean ACTH concentrations during the clamp phase of glucocorticoid feedback.
- Gender strongly influenced mean ACTH concentrations during recovery from exogenous cortisol infusion: women <men ($p<0.01$; KTCZ/low-dose cortisol arm, and $p<0.001$; KTCZ/high-dose cortisol arm) **(Fig. 2, Fig. 3)**
- Decreased ACTH recovery in women was associated with lower mean cortisol concentrations pointing to attenuated drive of ACTH outflow rather than cortisol hypersecretion as the sex-related mechanism.
- Both linear and nonlinear regression analyses confirmed markedly impaired ACTH recovery in women over time **(Table 2, Fig. 4)**

Table 1: Subject Characteristics

Subject Characteristics	Older Men	Older Women	P value
Number (n)	10	10	
Age (years)	60 ± 2.2	60.2 ± 2.2	0.90
BMI (kg/m^2)	28 ± 0.7	26 ± 1	0.08
Albumin (g/L)	44 ± 0.5	43 ± 0.7	0.29
Cortisol (mcg/dL)*	12 ± 1.1	12 ± 1.2	0.97
Estradiol (pmol/L)	84 ± 8.4	42 ± 5.5	<0.001
FSH (IU/L)	5.4 ± 0.5	74 ± 7.5	<0.001
LH (IU/L)	2.9 ± 0.5	26 ± 4.4	<0.001
Prolactin (pmol/L)	287 ± 23	326 ± 26	0.27
SHBG (nmol/L)	37 ± 5.4	59 ± 4.7	0.01
Testosterone (nmol/L)	18 ± 2.3	0.5 ± 0.1	<0.001
TSH (mIU/L)	1.8 ± 0.2	2.3 ± 0.5	0.21

Data are the mean ± SEM
* To convert to SI units (nmol/L) multiply by 27.6

Experimental Schema

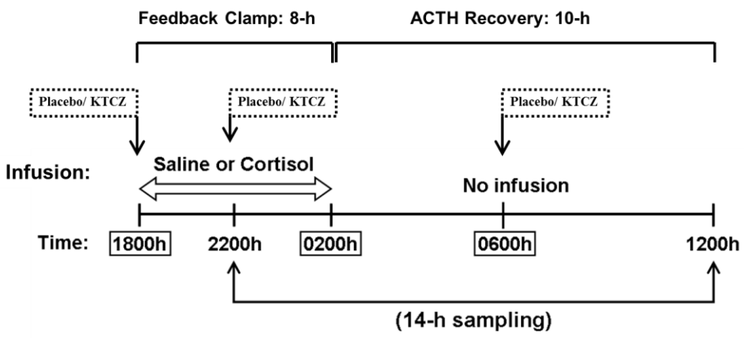

Fig 1. Schema of experiment

Gender impact on feedback and recovery of HPA axis

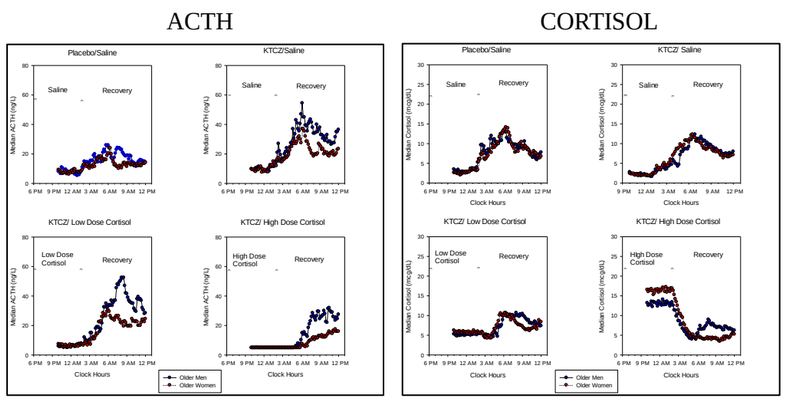

Fig 2. Each panel shows an individual interventional group (placebo/saline, KTCZ/saline, KTCZ/low-dose cortisol, KTCZ/high-dose cortisol). Data from men (●) and women (●) are displayed separately.
To convert ACTH ng/L to pmol/L, multiply by 0.2202, and cortisol mcg/dL to nmol/L, multiply by 27.6

ACTH: Initial and delayed recovery

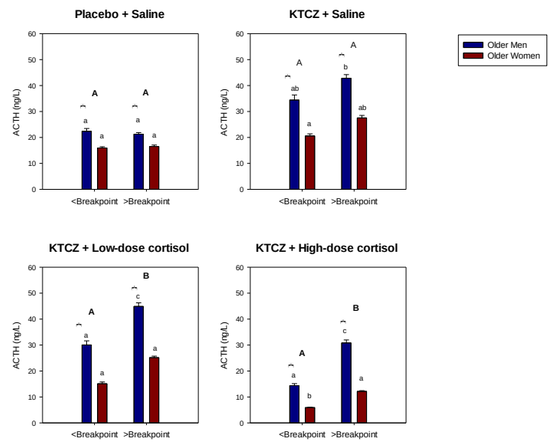

Fig 3.Different upper-case letters in the KTCZ/LDC and KTCZ/HDC arms denote significantly different mean ACTH concentrations, pre- (initial recovery) *and* post-breakpoint (delayed recovery). Different lower-case letters denote significant gender effects on mean ACTH concentrations both pre- and post-breakpoint during the recovery phase.

Table 2: ACTH recovery by gender

Linear Recovery Phase	ANCOVA (Mean ± SEM)		*Nonlinear* Curve fitting (Mean; 95% CI)		
Mean ACTH concentration (ng/L)	Men	Women	Mean ACTH concentration (ng/L)	Men	Women
Pre-Breakpoint			**Sigmoid Floor**		
Placebo/Saline	*22.4 ± 4.3*	*16 ± 1.5*			
KTCZ/Saline	*34.4 ± 6.2*	*20.6 ± 2.3*			
KTCZ/LDC	*30.0 ± 5.8*	*15.2 ± 1.3*	*KTCZ/LDC*	10.8; 6.7-15.2	8.9; 7-10.7
KTCZ/HDC	*14.4 ± 2.9*	*5.9 ± 0.9**	*KTCZ/HDC*	4.8; 2.7-5.9	4.4; 4.0-5.0
Post-Breakpoint			**Sigmoid Plateau**		
Placebo/Saline	*21.3 ± 3.5*	*16.5 ± 2.8*			
KTCZ/Saline	*42.8 ± 7.5*	*27.5 ± 4.4*			
KTCZ/LDC	44.9 ± 7.0	25.1 ± 2.4*	*KTCZ/LDC*	39.1; 36.9-41.2	23.8; 22.9-24.6*
KTCZ/HDC	30.8 ± 5.2	12.1 ± 0.9*	*KTCZ/HDC*	27.3; 26.2-28.3	16.2; 15.1-16.5*
Maximum ACTH concentration (ng/L)	**Mean; 95% CI**				
Placebo/Saline	43.1; 36.5-49.6	35; 27.3-42.7			
KTCZ/Saline	76.6; 39.3-114	62.1; 19.8-104			
KTCZ/LDC	71.4; 49.7-93	50.5; 33.3-67.3			
KTCZ/HDC	41.1; 27.5-57.7	22.2; 19.1-25.4*			

* p<0.05

Sigmoid fits of ACTH and cortisol recovery

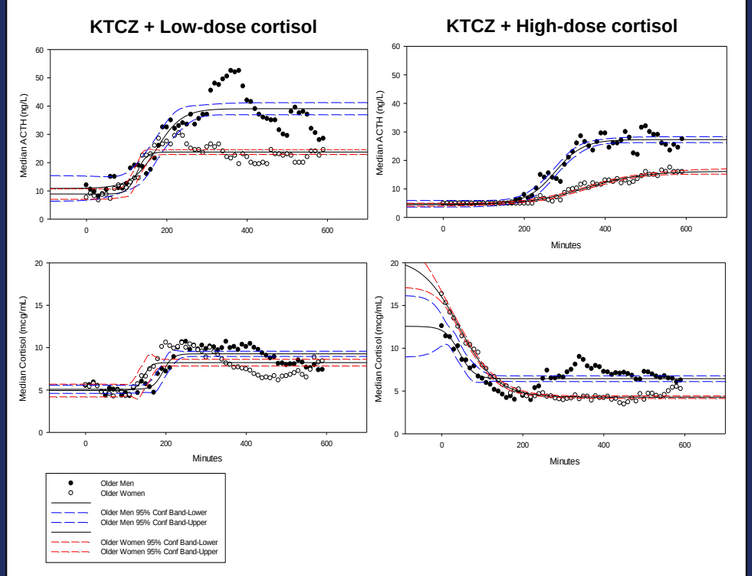

Fig 4. Time course of median ACTH (top) and cortisol (bottom) concentrations during recovery phase in the KTCZ/LDC arm (left) and KTCZ/HDC arm (right) in older men (blue) and women (red) evaluated via a (non-linear) 4-parameter sigmoidal curve model. The analysis yields estimates of the minimum (floor) and maximum (plateau) concentration along with 95% confidence bands. Time is shown in min. Zero time (x-axis) denotes 0200 h.

Discussion

- ACTH feedback escape was significantly lower in post-menopausal women compared with older men, after suppression by both low- and high-dose cortisol infusions
- In post-menopausal women, the sluggish return to baseline could result in longer overall exposure to stress hormones, compensating in part for lower absolute levels
- Intrinsic sex-related differences in the mechanistic regulation of the HPA axis could not be explained by differences in sex-steroid concentrations, as assessed by exploratory linear regression
- Our data suggest that testosterone possibly promotes HPA axis recovery after cortisol suppression, in view of the strong escape of ACTH in older men

Conclusions

- Gender determines the recovery of the hypothalamo-pituitary unit from cortisol-induced feedback, with attenuated responses in post-menopausal women
- The gender differences may have relevance to stress-related adaptations in the sexes