Abnormal reactions to environmental stress in elderly persons with anxiety disorders: Evidence from a population study of diurnal cortisol changes.

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Running title: cortisol in elderly persons with anxiety disorders

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ABSTRACT

Background: Cortisol secretion in elderly persons with anxiety disorders exposed to common stressful situations has not been evaluated.

Methods: Salivary-free cortisol levels were evaluated at 8, 15, and 22h, in 201 elderly subjects during stressful and non-stressful days. Psychiatric symptomatology was assessed by a standardized psychiatric examination (MINI).

Results: Elderly subjects without psychiatric disorder showed a sustained increase in cortisol secretion several hours after the exposure to a stressful situation. In comparison, subjects with anxiety disorders showed a greater increase in cortisol secretion in the stressful situation, with lowered recuperation capacity. This effect was dose-dependent as a function of anxiety co-morbidity. Persons reporting lifetime major trauma with intrusions exhibited lowered continuous basal cortisol associated with efficient recuperation capacity. Independently of psychopathology, women appeared more reactive to stressful environmental conditions.

Limitations: Exclusion of institutionalized persons and benzodiazepine users may have led to sampling of less severe anxiety symptoms.

Conclusions: Dysregulation of the hypothalamic-pituitary-adrenal axis was observed in elderly persons with anxiety disorders experiencing environmental stress. A common pattern of up-regulated diurnal cortisol secretion was observed in anxious subjects with lifetime and current anxiety disorder irrespective of sub-type (generalized anxiety, phobias) suggesting a stable trait and a common "core" across disorders. Elderly persons who had experienced trauma with subsequent intrusions showed a distinct pattern with down-regulated activity.

Key words: HPA axis, stress, anxiety disorders, traumatism, elderly.

1. Introduction

Generalized anxiety disorder (GAD) and phobia are frequent in the general population (Krasucki et al., 1998). Some experimental studies in young adults have linked these disorders to underlying changes in the hypothalamic-pituitary-adrenal (HPA) axis, resulting in an abnormal response (hypercortisolemia) to acute stress (Alpers et al., 2003; Condren et al., 2002; Furlan et al., 2001) but not consistently (Connor and Davidson, 1998; Young et al., 2004a)). This variability may be attributable to the nature and duration of the stressors (Glynn et al., 2002; Haynes et al., 1991).

Elderly persons are exposed to higher rates of life events than younger adults. Their biological response to experimental stress may be prolonged (Deuschle et al., 1997; Van Cauter et al., 1996; Wilkinson et al., 2001) suggesting modifications to underlying stress physiology. Previous experimental studies have generally used artificial, acute stimuli to induce stress, so little is known about cortisol secretion in naturalistic conditions especially in the more vulnerable group of elderly persons with anxiety disorders. The present study investigates diurnal cortisol secretion in a community cohort exposed to continuous low-grade naturalistic stress (a half-day hospital visit) contrasted with a quiet day at home as a function of anxiety disorder.

2. Methods

2.1. Study population

Subjects (n=261) were selected by random sampling from the electoral roles (Ritchie et al., 2004), excluding cases of dementia and persons being treated with medication likely to modify cortisol levels (glucocorticoids, hormone replacement therapy, benzodiazepines).

2.2. Diagnostic instruments

A standardized psychiatric examination validated within the French general population (Lecrubier et al., 1997); the Mini International Neuropsychiatric Interview MINI (French version 5.00), was used to detect psychiatric symptomatology according to DSM-IV criteria (American

Psychiatric Association, 1994).

2.3. Cortisol measurement

Subjects were instructed not to drink, eat or smoke for at least 30mn before saliva collection and to start the protocol at least 1h after awakening (mean time 1.5±0.8h) and subsequently twice with a 6-7h interval (the last sample being collected before midnight), recording the exact time. Mean values for sampling were 8.8±0.3, 15.7±0.7 and 21.7±0.6h.

Cortisol levels were determined from saliva collection (Hellhammer et al., 1987) by direct radioimmunoassay (Diagnostic Systems Laboratories-Webster, Texas). For less than 5% of the samples, the values were lower than the detection limit (10ng/dl) and were replaced by a value corresponding to the threshold value divided by two. When adequate volume could not be provided subjects were excluded from the analysis. Thirty six subjects with an atypical cortisol baseline profile (flat pattern or abnormal time peak) were excluded from the sample. The present study has been conducted on 201 subjects showing a typical pattern at baseline.

2.4. Baseline and environmental stress conditions

Subjects were allowed to decide wake up and sleep times and to collect samples when convenient. Participants were encouraged to carry on their normal daily activities with limited physical exertion in order to maximize ecological validity. Samples were taken at the hospital ("stressful situation") where a lengthy clinical examination (between 08-11h AM) was undertaken involving recognized psychosocial stressors, (*e.g.* psychiatric examination, cognitive testing, clinical evaluation, blood collection), and a subsequent quiet day at home (baseline condition).

2.5. Statistical analysis

Since the distribution of raw cortisol is typically skewed and the diurnal profile may be approximated by an exponential curve, raw values were log-transformed[1]. Given the non-fixed time sampling protocol, AUC were standardized and calculated by trapezoidal estimation between

[1] An absolute difference (δ) between two LnC values thus corresponds to a ($e^{\delta}-1$) x100 variation (expressed as %) on initial (non log-transformed) cortisol concentrations.

08h and 22h for each subject (extrapolating values from the equation of the regression line of the three-cortisol values on the hour of sample collection). Group comparisons were carried out using Student's t-test and analysis of variance for categorical explanatory variables. Individual stress responses comparing home and hospital cortisol values were performed using paired t-tests.

Comparison of cortisol profiles on stressful and basal situations was also carried out using a hierarchical mixed model. This takes into account individual differences, differences with time within the day and differences between days (3 levels). Anxiety disorders were entered individually into the model to assess their impact on differences in cortisol levels between the two sampling days. Time was entered both as a fixed and random effect, allowing for individual random differences form the sample mean cortisol value according to time of day.

All analyses were stratified by sex. p values <0.05 were considered to be statistically significant. Data were analyzed using SAS version 8.2 (Cary, NC).

3. Results

Subject characteristics are shown in **Table 1.** Cortisol concentrations and AUC were higher and slope flatter in women, however no age effect was observed (data not shown).

3.1. Diurnal cortisol and anxiety disorder in women

Women with and without lifetime GAD did not differ on baseline measures (**Table 2A**). Following stress, paired comparisons indicate an increase in AUC and LnC, which was significant at 15h and 22h, for both groups. Group comparisons showed that on the stressful day LnC at 15h and 22h and AUC were significantly higher in women with GAD (by 7.9%, 12.6% and 8%, respectively) as also suggested examining relative differences. A similar pattern was observed for the 21 women reporting lifetime phobia (data not shown). Mixed models further indicate a significant interaction between sampling day and GAD (F=8.36, p=0.004) or phobia (F=6.79, p=0.009).

For all lifetime anxiety disorders, a gradual increase in AUC, LnC_{15h}, and LnC_{22h} and slope

flattening were observed on the stressful day along with the number of associated anxiety symptoms (p<0.001) (data not shown). Subjects with current anxiety disorders (n=17) showed similar patterns to those with past anxiety disorders.

While only one woman reported lifetime PTSD, eight women reported previous severe trauma with subsequent distressing intrusions ("traumatized" group), thus meeting criteria A and B for DSM-IV PTSD. Their AUC, LnC_{15h}, and LnC_{22h} were significantly lower at baseline (by 13.3, 13.3, and 31.6%, respectively) and the slope steeper (by 43.8%) compared to “non-traumatized” women (**Table 2B**). No differences were observed on the stressful day between “traumatized” and “non-traumatized” women, suggesting the former had developed an efficient compensatory response (see relative differences or paired comparisons). Mixed models indicate an interaction between sampling day and trauma with intrusions (F=4.59, p=0.03). The value for the interaction between time and sampling day was significant only for "traumatized" subjects (F=4.69, p=0.038) and that between time and trauma for the day at home only (F=5.45, p=0.022).

3.2. Diurnal cortisol and anxiety disorder in men

No significant differences between men with and without lifetime anxiety disorder were observed on the baseline measure. In the stressful situation, slope was flatter (by 22.2%, p=0.01), LnC_{22h} higher (by 11.1%, p=0.04), and ΔLnC_{8h} lower (p=0.04) in the anxious than in the non-anxious group (data not shown**)**. Mixed models indicate an interaction between time and day which was significant only for subjects reporting lifetime anxiety disorders (F=4.97, p=0.029) and between time and anxiety for the hospital-day only (F=7.07, p=0.009).

In men with a history of trauma with intrusions**,** LnC_{8h} tended to be higher by 7.4% (p=0.07) and slope steeper by 29.4% (p=0.07) compared to “non-traumatized” men suggesting a more rapid decline rate under baseline conditions. A high increase was observed in ΔLnC_{22h}

(52.2% compared to 17.2% in controls, p=0.01), giving recovery levels after stressful situation similar to that of the "non-traumatized" group. Mixed models suggested a time/trauma interaction (at home) and a time/day interaction in "traumatized" subjects .

4. DISCUSSION

4.1. Methodological considerations and study design

This naturalistic study explored the effect of exposure to a common stressful situation in the morning on subsequent diurnal cortisol levels at home. Our findings are more directly comparable to “post-event processing” i.e. the prolonged cognitive processing period following social interaction (Fehm et al., 2007) than to "recovery period" studies conducted 1-2h after pre-test basal cortisol evaluation (Kudielka et al., 2004; Seeman et al., 1995).

In subjects both with and without psychiatric disorder, enhanced cortisol levels were observed from 4h to 11h after the stressful situation. No study has investigated long-term activity of the HPA axis following stress, notably during the “post-event processing” period. However, delayed recovery and sustained recurrent elevations in physiological autonomic nervous system responses to emotional tasks have been observed in healthy adults, partly related to ruminations (Glynn et al., 2002). Ruminations, which may last several days after social exposure (Fehm et al., 2007), are an important psychological component of anxiety whose effect may be exacerbated in the elderly.

4.2. Anxiety disorder and exposure to environmental stress

Lifetime anxiety disorder in this community sample is common (27%). Subjects with anxiety disorder show baseline cortisol levels similar to those without anxiety disorder. Men with anxiety disorders showed a secretion increase following stressful situation, but with a slower decline rate compared to non-anxious men. In women a dose-effect was observed; the higher the anxiety co-morbidity, the greater the increase in total secretion and the lower the recovery capacity following the stressful situation.

Cortisol secretion in anxious subjects under stress conditions has only been evaluated in young adults, generally during an acute stressful challenge, with inconsistent results. Condren et al found an increase in cortisol secretion in patients with phobia compared to controls but not during the 90 mn recuperation period (Condren et al., 2002). Furlan et al reported that phobic patients responded less frequently to psychosocial stress than controls, but with a higher increase in cortisol secretion on a stress-test (Furlan et al., 2001). Young et al reported normal cortisol responses to the Trier Social Stress Test in subjects with pure anxiety or pure mood disorders, whereas they observed a greater ACTH and cortisol (trend) response to the stressor, in depressed subjects with co-morbid anxiety (Young et al., 2004a). In our study the proportion of subjects reporting current anxiety disorder with co-morbid major depression was too low (0.5%) to affect the results. For lifetime anxiety disorder, the same cortisol pattern was observed irrespective of depression co-morbidity (unpublished data).

4.3. Sub-syndromic PTSD

In everyday functioning, elderly traumatized persons have continuous basal low cortisol levels with a more rapid decline than controls. Following stress, accelerated secretion was observed to reach “normal” levels of cortisol excretion. This pattern is specifically associated with PTSD intrusive symptoms, suggesting that both intrusions and cortisol changes could be indicative of trauma severity.

Low cortisol concentration in PTSD has been frequently reported (Boscarino, 1996; Mason et al., 1986; Neylan et al., 2005; Rasmusson et al., 2003; Yehuda, 2001; Yehuda et al., 1995) although not systematically (Baker et al., 2005; Maes et al., 1998; Pitman and Orr, 1990; Young et al., 2004b). In our sub-syndromic group with intrusive symptoms, we found a similar pattern of lowered cortisol secretion at baseline suggesting a continuum with PTSD. Low cortisol concentration has also been reported in non-PTSD subjects living under conditions of chronic/prolonged stress (maintained by intrusions and recurrent memories (Baum et al., 1993)) which may modify HPA axis functioning (Hellhammer and Wade, 1993). Our observations are

compatible with this theory. Response increase in the stressful situation suggests efficient HPA axis reactivity (Yehuda et al., 1996).

Recent studies have demonstrated that glucocorticoid administration can inhibit the expression of PTSD symptoms in young adults (Schelling et al., 2004a; Schelling et al., 2004b), notably intrusive symptoms (Aerni et al., 2004) by inhibiting excessive retrieval of traumatic memories (Aerni et al., 2004; de Quervain et al., 1998; de Quervain et al., 2000). Our findings of low cortisol levels related to intrusive symptoms support these observations. Evaluating glucocorticoid treatment in subjects with low basal cortisol could thus be an alternative to psychotropic medication (Schuder, 2005).

4.4. Limitations and strength

Although this population study had to be limited to 3-salivary measures, the basal characteristics of cortisol secretion are similar to previous studies with more frequent sampling (Ice et al., 2004). The random selection of subjects, the systematic return of saliva samples by all subjects and the choice of a non-fixed time sampling protocol (known to improve compliance (Jacobs et al., 2005)), suggest our findings to be representative of naturalistic conditions. However, one limitation could be that the current anxiety syndromes may have been less severe as benzodiazepine use constituted an exclusion criterion. We aimed to examine differences between baseline and naturalistic exposure to stress rather than to a single experimental stressor; randomization of days not being feasible, we commenced with stress exposure, thus obtaining maximal contrasting conditions (avoiding novelty/anticipatory effects on baseline measures). We also controlled for eating, drinking, smoking, and physical exertion. Subjects did not report any particular potential additional stressors on the day they performed sampling. Although our study could be considered exploratory, the differences observed more likely result from the effect of anxiety disorders on the response to the stressor. Despite multiple analyses, Bonferroni corrections were not considered necessary, the patterns of cortisol changes being consistently observed for both sexes and using both general linear and hierarchical mixed model analyses.

4.5. Implications of the study

In normal everyday functioning elderly persons have a pattern of daytime cortisol secretion, which is not affected by either age or anxiety disorders. Everyday stress induces a higher increase in cortisol secretion in persons with anxiety disorders than in non-anxious persons, and slower recovery rates, probably related to post-event processing. Women appear more reactive to stressful environmental conditions than men, perhaps explaining their overall heightened vulnerability to anxiety disorders. Similar changes were observed in subjects with past anxiety disorder suggesting this vulnerability to be a stable trait. A similar pattern of alteration is observed in anxiety disorders when taken together or by sub-type (phobias or GAD), suggesting a common "core" with respect to HPA axis dysregulation. Rate of increase in cortisol secretion may also be a putative marker of anxiety severity (associated with increased co-morbidity). Do these differences in HPA axis physiology constitute individual vulnerability to psychopathology? Follow-up studies are required to further examine the relationships between HPA axis changes and time of onset of psychopathology.

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Table 1

General characteristics of the cortisol study participants

	Subjects (N =201)
Female gender (%)	43.8
Mean age (SD)	72.9 (4.5)
Low Education level[a] (%)	47.3
Current Smoking	6.0
MMSE score below 24 (%)	4.5
Body Mass Index in kg/m^2 (mean (SD))	25.6 (3.6)
CURRENT MAIN PSYCHIATRIC DISORDERS	
Major Depressive Episode (%)	1.0
Generalized Anxiety Disorder (%)	3.0
Phobia (%)	10.1
PTSD (%)	0.5
At least one anxiety disorder (%)	13.7
Current comorbidity (Anxiety disorder + MDE) (%)	0.5
LIFETIME MAIN PSYCHIATRIC DISORDERS	
Major Depressive Episode (%)	18.4
Generalized Anxiety Disorder (%)	11.1
Phobia (%)	17.4
Severe trauma (DSM-IV[b]) (%)	29.9
Sub-syndromic PTSD (DSM-IV[b]) (%)	9.1
PTSD (%)	1.5
At least one anxiety disorder (%)	26.9
Comorbidity (Anxiety disorder + MDE) (%)	10.1

[a] Corresponding to 9 years of schooling or less.

[b] Sub-syndromic PTSD corresponds to subjects meeting criteria A and B for DSM-IV PTSD, *i.e.* having reported previous severe trauma with subsequent distressing intrusions.

Table 2: Cortisol levels under basal and stressful conditions for women according to the absence (0) or presence (1) of anxiety disorder.

2A: Lifetime GAD

Cortisol parameters	GAD (0: n=68) (1: n=18)	GROUP COMPARISONS								PAIRED COMPARISONS
		Baseline			Stress			Relative difference (Δ)**		
		mean	SD	*p*	mean	SD	*p*	%	*p*	*p*
LnC_{8h}*	0	5.53	0.59	0.51	5.67	0.67	0.11	3.6	0.35	0.09
	1	5.63	0.68		5.97	0.76		7.2		0.13
LnC_{15h}*	0	4.38	0.62	0.97	4.58	0.51	0.01	5.8	0.01	< 0.001
	1	4.38	0.65		4.94	0.62		14.4		0.001
Ln_{22h}*	0	3.24	0.97	0.65	3.48	0.74	0.03	17.9	0.10	0.01
	1	3.13	1.05		3.92	0.88		37.6		0.002
slope	0	-0.16	0.07	0.43	-0.16	0.07	0.59	14.5	0.49	0.49
	1	-0.18	0.09		-0.15	0.08		1.4		0.17
AUC	0	61.39	8.62	0.97	64.08	7.14	0.01	5.8	0.01	< 0.001
	1	61.30	9.05		69.21	8.69		14.4		0.001

2B: Lifetime Traumatism and Intrusions

Cortisol parameters	Trauma + Intrusions (0: n=78) (1: n=8)	GROUP COMPARISONS								PAIRED COMPARISONS
		Baseline			Stress			Relative difference (Δ)		
		mean	SD	*p*	mean	SD	*p*	%	*p*	*p*
LnC_{8h}	0	5.56	0.60	0.56	5.76	0.72	0.38	4.4	0.80	0.03
	1	5.43	0.71		5.53	0.35		3.0		0.70
LnC_{15h}	0	4.44	0.60	0.01	4.68	0.57	0.24	6.6	0.03	<0.001
	1	3.85	0.59		4.44	0.35		17.3		0.03
LnC_{22h}	0	3.32	0.95	0.003	3.59	0.80	0.39	17.3	0.002	0.002
	1	2.27	0.81		3.34	0.59		67.7		0.02
slope	0	-0.16	0.07	0.02	-0.15	0.07	0.95	15.0	0.18	0.50
	1	-0.23	0.07		-0.16	0.05		-19.9		0.06
AUC	0	62.12	8.37	0.01	65.46	7.91	0.24	6.6	0.03	<0.001
	1	53.85	8.31		62.11	4.96		17.3		0.03

*Time concentrations correspond to the Ln of cortisol concentration expressed as ng/dl. **Corresponds to the mean of the ratios [(hospital – home)/ home] expressed as %.