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Cortisol levels during human aging predict hippocampal atrophy and memory deficits

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Elevated glucocorticoid levels produce hippocampal dysfunction and correlate with individual deficits in spatial learning in aged rats. Previously we related persistent cortisol increases to memory impairments in elderly humans studied over five years. Here we demonstrate that aged humans with significant prolonged cortisol elevations showed reduced hippocampal volume and deficits in hippocampus-dependent memory tasks compared to normal-cortisol controls. Moreover, the degree of hippocampal atrophy correlated strongly with both the degree of cortisol elevation over time and current basal cortisol levels. Therefore, basal cortisol elevation may cause hippocampal damage and impair hippocampus-dependent learning and memory in humans.

The hypothalamic-pituitary-adrenal system is highly sensitive to everyday challenges in animals and humans[1]. Acute stress triggers release of glucocorticoids, which then feed back onto specific brain regions to inhibit further release[2]. In addition to pituitary and hypothalamic sites, the limbic system, particularly the hippocampus, has been implicated in the regulation of glucocorticoid activity[2]. Although glucocorticoid responses to stress are essential for survival, prolonged glucocorticoid elevation can present serious health risks, including diabetes, hypertension, hyperlipidemia, hypercholesterolemia, arterial disease, amenorrhea, impairment of growth and tissue repair and immunosuppression[3].

Elevated glucocorticoids are linked with hippocampal pathology in aging rodents[4]. Basal plasma corticosterone levels among aged rats correlate significantly with hippocampal degeneration and spatial learning deficits[5,6]. Elevated plasma corticosterone levels are found only in aged rats with spatial memory deficits and not in aged rats with normal spatial memory[7]. Cumulative exposure to high glucocorticoid levels throughout life disrupts electrophysiological function, leading to atrophy and ultimately death of hippocampal neurons, all of which can cause severe cognitive deficits[4] in hippocampus-dependent learning and memory[8]. Adrenalectomy at mid-life, with low-level glucocorticoid replacement, attenuates hippocampal degeneration and cognitive decline in rats[5], suggesting that elevated glucocorticoid levels directly contribute to the development of cognitive impairments. Together, these results strongly suggest that glucocorticoid elevation partly accounts for individual differences in age-related hippocampal damage and memory defects in rodents.

Recent studies in patient populations have suggested a similar relationship in humans . In Cushing's syndrome, which causes prolonged cortisol elevation, hippocampal volume correlates negatively with plasma cortisol levels, and positively with scores on verbal memory tests[9]. Alzheimer's patients show an inverse relationship between mean 24-hour cortisol levels and severity of cognitive decline, which is associated with progressive hippocampal degeneration[10]. Here we ask whether this relationship extends to healthy elderly human subjects.

For five to six years, we measured basal plasma cortisol levels annually over a 24-hour period in 51 aged healthy volunteers[11]. To estimate the cumulative exposure to glucocorticoids, a simple regression analysis on plasma cortisol levels for each subject was conducted using year as the independent variable and the integrated 24-hour cortisol concentration as the dependent variable. The slope of the regression line (termed "cortisol slope") was chosen as the measure of the dynamic change in adrenal activity so as to differentiate patients whose cortisol was decreasing from those whose cortisol was increasing with time[11]. We found considerable variation in plasma cortisol levels, as well as clear evidence for three subgroup patterns: progressive increase in cortisol levels with currently high basal cortisol levels (termed "increasing/high cortisol"), progressive increase in cortisol levels with currently moderate cortisol levels ("increasing/moderate cortisol"), or progressive decrease in cortisol levels with currently moderate cortisol levels ("decreasing/moderate cortisol"). Both acute and chronic cortisol elevations induce cognitive deficits in human populations[12,13].

We measured the environmental validity of our yearly laboratory cortisol measures by taking salivary samples for cortisol analy-

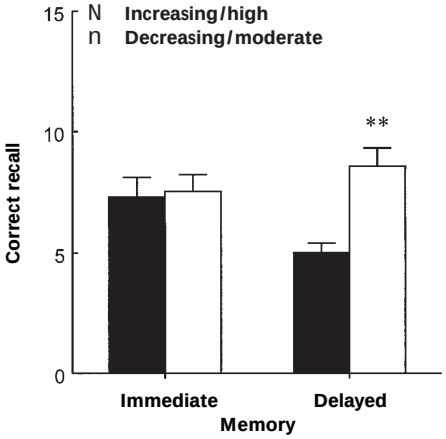

Fig. 1. Mean (± SEM) correct recall of the increasing/high and decreasing/moderate cortisol groups on the immediate and delayed memory task. *Significant group difference at $p<.05$.

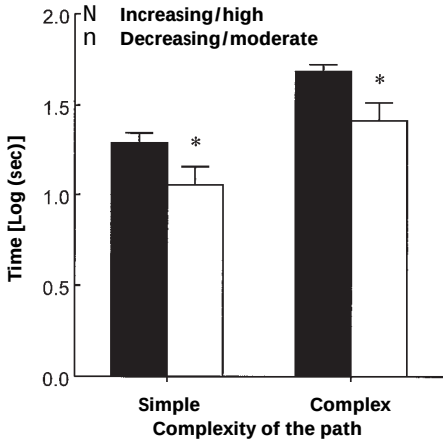

Fig. 2. Mean (±SEM) time [log(sec)] for the increasing/high and decreasing/moderate cortisol groups to find their way through a human maze for a simple and a complex path. *Significant group differences at $p<.05$.

sis at the subject's home, four times a day, over a 30-day period. These cortisol levels clearly differentiated the subgroups over this longer period of time (*Int. Soc. Psychoneuroendocrinology Abs*. 92, 1996). In this study, subjects with increasing/high cortisol also reported higher feelings of stress than the decreasing/moderate cortisol group over the 30-day period. Finally, the increasing/high cortisol group showed significant impairments in hippocampus-dependent forms of memory compared to the other groups[14]. Performance on tests of hippocampus-independent memory was similar for all three groups of subjects[14]. These findings suggest that increased glucocorticoid levels can influence hippocampus-dependent memory in aged humans. The present study tests whether prolonged cortisol elevation and memory impairment in normal elderly humans correlate with a significant decrease in hippocampal volume, as reported in the animal literature.

Results

We performed magnetic resonance imaging (MRI) on a subgroup of subjects from the increasing/high cortisol group, and the decreasing/moderate cortisol group. Given the increased variability in cortisol secretion and cognitive function during human aging[11,12,14], we used these two extreme groups to assess the magnitude of the difference in hippocampal volume in conditions of normal versus impaired glucocorticoid activity during human aging. As the hippocampus is implicated in performance of several other cognitive tasks[8], particularly those sensitive to the time-limited[15] and spatial[16] aspects of memory, we also measured these two groups on an immediate versus delayed memory task and on spatial memory with a human maze.

Memory

Using a repeated measures ANOVA with group as the between-subjects factor and immediate and delayed memory as the repeated measure variable, we observed a main effect for group [$F(1,7) = 7.9$, $p<0.05$] and a significant interaction effect [$F(1,7) = 17.5$, $p<0.01$]. Simple effects performed on this interaction revealed that the increasing/high cortisol group showed significant impairments on delayed recall ($p<0.02$; see Fig. 1), although the groups did not differ on tests of immediate memory.

Using a similar model for performance on the spatial memory test with time [log(sec)] required to follow the simple versus complex path as the repeated measure variable, we found main effects for both group [$F(1,8) = 8.4$, $p<0.05$] and path complexity [$F(1,8) = 64.6$, $p<0.001$] with no interaction between these two variables. The increasing/high cortisol group took significantly longer to recall and follow either the simple or the complex path compared to subjects from the decreasing/moderate cortisol group (Fig. 2).

Hippocampal volume

We compared the increasing/high cortisol and the decreasing/moderate cortisol groups over the volume of the hippocampus, parahippocampal gyrus, fusiform gyrus, the middle-inferior, and the superior temporal gyri. Two findings were noteworthy. First, the total hippocampal volume of the increasing/high cortisol group was significantly reduced by 14% in comparison to that of decreasing/moderate cortisol group [$t(9) = 25.1$, $p<0.001$, Table 1 and Fig. 3]. Second, this effect was unique to the hippocampus; we found no group differences in the volume of the parahippocampal and fusiform gyri, nor in the other temporal lobe structures analyzed (Table 1).

Table 1. MRI volumes for selected regions (right and left hemispheres combined, cm^3)

	Increasing/ High	Standard Error	Decreasing/ Moderate	Standard Error
Hippocampus	4.00*	0.08	4.54*	0.13
Parahippocampal Gyrus	5.50	0.44	5.42	0.47
Fusiform Gyrus	8.57	1.11	8.24	0.69
Superior Temporal Gyrus	21.07	1.15	19.06	1.59
Middle and Inferior Temporal Gyri	26.73	1.43	27.82	1.21
Head Size	278.68	14.72	273.78	8.29

*significant difference at p<0.001

Correlations among measures

The relationship between cortisol and hippocampal volume was examined by

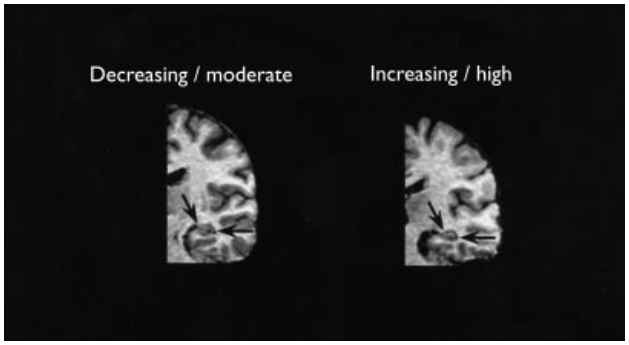

Fig. 3. Reformatted (perpendicular to the long axis of the hippocampus) coronal T1-weighted gradient echo coronal MRI image of the hippocampus (arrows on left side) at the level of the lateral geniculate body for representative increasing/high and decreasing/moderate subjects.

regression analyses. A significant correlation was found (r = -0.80, r^2 = 0.64, p<0.01; see Fig.4) between cortisol slope and hippocampal volume (left+right sum/hemi sum), as well as a significant correlation (r = -0.68, r^2 = 0.46, p<0.02) between current cortisol measure and hippocampal volume.

To compare these results to other studies that have linked hippocampal volume and delayed memory performance[17], we examined our data in a set of hierarchical regression models. No significant correlations were found between the principal measures (brain regions and cortisol slope) and either age, gender or education (p>0.1). Consequently, these measures were not included in our regression models as covariates. In the first step, we covaried out the effect of immediate memory as a baseline measure. We then entered either the volume or slope measurement. Of these two measures, only the hippocampal volume showed a significant relationship to delayed memory ($F_{change}(1,6)$ = 5.8, r^2_{change} = 0.30, p<0.05). We further tested the anatomic specificity of the hippocampus relative to the other temporal lobe regions. The middle inferior temporal lobe was the only other region to be significantly related to delayed memory (F_{change} (1,6) = 7.9, r^2_{change} = 0.34, p<0.05). In a final set of regression models, we tested the unique variance attributed to the hippocampus and middle inferior temporal lobe relative to delayed memory. In this model, we entered immediate memory and either the hippocampus or middle inferior temporal lobe in step 1 and the second region in step 2. We found that although each region accounted for a significant proportion of variance in delayed memory, neither added an appreciable amount of variance to the other region. We then examined the relationship of cortisol slope to each of the temporal lobe regions separately. Only the hippocampus exhibited a relationship to cortisol slope (r = -0.80, p<0.01, two-tailed).

Discussion

The present study revealed that elderly human subjects showing increasing cortisol levels over years with currently high cortisol levels are impaired on hippocampus-dependent memory and have a 14% reduction in hippocampal volume, compared to elderly subjects showing decreasing cortisol levels over years with currently moderate cortisol levels. These results are in accordance with animal studies showing that cumulative exposure to high glucocorticoids has functional and structural effects on the hippocampus[6,7,8]. Studies of brain changes associated with dementia in later life show an anatomically specific relationship between hippocampal volume and memory. These observations have been extended to elderly populations showing mild cognitive impairments (MCI)[18]. Interestingly, the magnitude of the decrease in hippocampal volume in the increasing/high cortisol group was comparable to that previously reported for elderly subjects with age-related MCI[18]. As our subjects were originally selected on the basis of differences in cortisol secretion[11], rather than on differences in cognitive performance, we suggest that increases in cortisol secretion in later life may initiate MCI and/or MCI-related hippocampal atrophy.

Our findings are consistent with the idea that exposure to progressively elevated glucocorticoid levels eventually compromise hippocampal integrity and thus performance on hippocampus-dependent cognitive tasks[7,8]. The decrease in hippocampal volume was correlated with both the current basal cortisol levels and the cortisol slope, which reflected changes in plasma cortisol levels over the past five years. Hence, hippocampus-dependent cognitive impairments are associated with a profile of progressively increasing basal cortisol and a currently elevated cortisol level.

The hippocampus is not only a target for glucocorticoids but is also involved in their regulation[2,4]. Lesions to the hippocampus are associated with increased basal glucocorticoid levels[19], and the hippocampus has been implicated in regulating glucocorticoid release during stress[20]. Thus, hippocampal atrophy is both a result of and a contributory cause of elevated basal glucocorticoid levels. This is embodied in the glucocorticoid cascade hypothesis for hippocampal aging[21], which proposes that hippocampal damage leads to increased circulating glucocorticoid levels, which in turn worsen the degree of hippocampal damage.

The effects of glucocorticoids on the hippocampus depend on concentration[4]. Normal basal levels of glucocorticoids facilitate hippocampal plasticity[22] and promote the survival of dentate gyrus granule cells[23], whereas elevated glucocorticoid levels are clearly associated with hippocampal dysfunction. These apparently contrasting effects can be understood in terms of the known differences in corticosteroid receptor subtypes[24]. Mineralocorticoid receptors bind glucocorticoids with a five- to ten-fold higher affinity than do glucocorticoid receptors[24]. Basal glucocorticoid levels act on the brain via mineralocorticoid receptors, whereas the compromising effects involve activation of a high percentage of glucocorticoid receptors[4]. Normal basal cor-

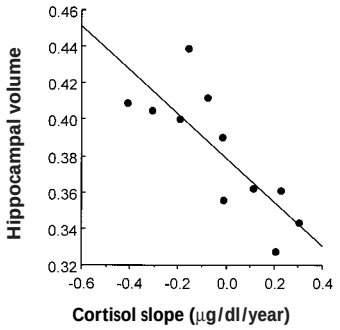

Fig. 4. Correlation between cortisol slope and hippocampal volume in 11 elderly human subjects.

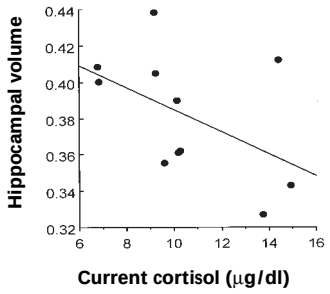

Fig. 5. Correlation between current cortisol levels and hippocampal volume in 11 elderly human subjects.

tisol levels, such as those seen in the decreasing/moderate cortisol group, primarily activate mineralocorticoid receptors and facilitate hippocampal long-term potentiation[22], a synaptic model of memory. In contrast, the elevated cortisol levels of the increasing/high cortisol group, which correspond to the normal circadian peak value and even approximate those levels seen during stress, would activate a larger proportion of glucocorticoid receptors, serving not only to negate the effects of mineralocorticoid receptor activation[4] but also to promote the debilitating glucocorticoid receptor effects on hippocampal function, including a dampening of long-term potentiation[25,26].

We propose that decreased hippocampal volume is associated with both the current high cortisol level and the increases in cortisol levels over the years. As in the rodent hippocampus, prolonged exposure to elevated glucocorticoid levels, along with elevated excitatory amino acid activity, could directly contribute to the decrease in hippocampal volume observed in the increasing/high cortisol group. Glucocorticoids serve to enhance calcium-dependent afterhyperpolarization in hippocampal neurons, which dampens responses to excitatory input[27]. Chronic elevations in circulating glucocorticoid levels are associated with decreased long-term potentiation or primed-burst potentiation in rat hippocampus, and these effects are reversed by adrenalectomy or by administration of a glucocorticoid receptor antagonist[22,27]. Sustained exposure to elevated glucocorticoid levels or repeated psychological or psychosocial stress also produces atrophy of hippocampal pyramidal neurons in the rat and tree shrew, and these effects are attenuated by NMDA receptor blockers and by phenytoin, which blocks sodium and T-type calcium channels[28]. In addition, chronic stress, which persistently elevates glucocorticoid levels, attenuates the normally occurring neurogenesis in hippocampal dentate gyrus of adult monkeys, a process that is thought to be necessary to sustain a constant level of neuron density in this region[29]. Finally, in the extreme, glucocorticoids have been shown to enhance hippocampal neuron loss following treatment with excitotoxins, and again this effect has been associated with increases in intracellular calcium levels[30]. Together, these various effects could account for the decreased hippocampal volume observed in the increasing/high cortisol group. It remains to be seen whether hippocampal volume reduction in these subjects reflects a reversible atrophy or an irreversible neuronal loss and whether these hippocampal changes will lead to further impairments of cognitive function, including dementia, later in life.

Methods

POPULATION. Subjects for the Study for Aging of the Douglas Hospital in Montreal are solicited from ads in the local media. The medical status of each subject is determined annually by a complete physical examination including ECG, EEG, CAT scan, and a battery of laboratory tests for kidney, liver, and thyroid functions, hemogram, vitamin B12, folate levels, as well as a neuropsychological assessment (for a complete description of these data, see refs. 11 and 14). Informed consent is obtained from all subjects. Our previous studies demonstrate that there is no change in the circadian rhythm nor CBG levels in these subjects[11], nor are there any differences between men and women with regard to cortisol history or any other variables tested[11].

The sample used in the present study was composed of 11 subjects. Six of them were from the increasing/high cortisol group (mean age: 76.5 ± 4.3; mean education level: 10.5 ± 2.3 years; current cortisol levels at the time of MRI testing: 12.8 µg/dl ± 3.1; cortisol slope: 0.56 µg/dl/year). The other five subjects were from the decreasing/moderate cortisol group (mean age: 70.8 ± 7.2; mean education level: 12.0 ± 4.3 years; current cortisol levels at the time of MRI testing ; 9.1 µg/dl ± 2.9; cortisol slope: -0.95 µg/dl/year). There were no significant differences between age or education level in the two groups ($p>0.1$). The increasing/high cortisol group showed significantly higher current cortisol levels ($p<0.05$) and a significantly higher cortisol slope over years ($p<0.05$) compared to the decreasing/moderate cortisol group.

CORTISOL MEASUREMENT. Subjects are tested annually for plasma cortisol levels over a continuous 24-hour period with sampling each hour. Blood samples are centrifuged at 2500 rpm for 10 min at 0-40°C, frozen, and stored at -200°C until assayed. The validation of the subgroups has been described in detail[11], and subjects were selected based on the groupings we described[14]. For plasma cortisol samples, a 300 µl aliquot of the extract was assayed in duplicate using [^{3}H]cortisol as tracer and a highly specific cortisol antibody (B-63 from Endocrine Sciences, Tarzana CA). This antibody cross-reacts less than 4% with deoxycortisol or deoxycorticosterone, and less than 0.5% with other adrenal steroids. Intra- and inter-assay variability are 4% and 6% respectively.

MEASURES OF MEMORY. Immediate and delayed memory was measured by presenting 15 non-complex line drawings of everyday objects taken from a standardized set of pictures controlled for name agreement, image agreement, familiarity, and visual complexity. The set of images was moderately prototypic [21.56 ± 4.52], and the characteristics of the images extracted from the Snodgrass and Vanderwart standardized set were as follows : Name Agreement, 90.33% ± 8.51; Image Agreement, 3.78± 0.67; Familiarity, 3.78±0.89; Complexity, 2.77±0.82. The image set was developed by I. Lussier, Univ. Montreal (1992). The subject was presented with the 15 line drawings for 3 seconds each and asked to name the object. Subjects were then asked to verbally recall as many line drawings as possible, immediately after the presentation or 24 hours later. The number of pictures correctly recalled on each occasion served as the dependent measure. One subject from the increasing/high cortisol group and one from the decreasing/moderate cortisol group were not available for 24-h delayed memory testing, so results of analyses (see below) are based on the remaining nine subjects.

Spatial memory function was measured in the same individuals using a human maze that allows for control of the difficulty level of the task and limits extraneous perceptual factors, which could interfere with the measure of spatial cognition. This human maze was designed by Dr. Romedi Passini from the Dept. of Architecture at the University of Montreal. The surface area of the maze was 1,500 square feet and the walls were 6 feet high, with no extraneous cues, either on the floor or on the ceiling. The passages corresponded to a small domestic corridor of one meter in width. The subject was shown a path by following the experimenter through the maze and was then required to reproduce the path on his/her own by walking through the maze. The subjects had to learn a simple and a complex path. The complexity of the path was determined by the number of decision points in the path. A decision point is an intersection in the maze at which the subject must make a decision (turn left, right or go straight ahead). The simple path required three decisions, and the complex path required five decisions. All subjects learned the notion of a point of decision using a smaller maze of 500 square feet that was built beside the first maze, which also served to reduce the novelty of the procedure. The time taken to find the correct path served as the measure of spatial memory function. Subjects presented equivalent walking pace when measured on a pilot study, using the smaller human maze. One subject from the decreasing/moderate cortisol group needed a cane for walking and was thus not tested on the human maze. The results of the analyses are thus based on the remaining 10 subjects.

MRI MEASUREMENTS. We acquired 124 sagittal T1-weighted (TR = 24, TE = 5, FA = 45) gradient echo images using a 1.5 GE Sigma imager. The MRI volumetric method is similar to that reported[24]. Sagittal images were acquired with a 24 cm field of view using a slice thickness of 1.2 mm without gaps and a 256 X 192 matrix. Scans were reformatted at a 2 mm slice thickness in the coronal plane for the anatomical work. In reformatting the images, we identified the anterior-posterior plane corresponding to the band of gray matter at the junction of the left hippocampus and parahippocampal gyrus and set the plane of coronal acquisition perpendicular to this. Using MIDAS image analysis software (Tsui, M.H. Multimodal Image Data Analysis System (MIDAS). Version 1.0, unpublished

manual, 1995) developed at NYU in-house with a Sun Sparc workstation (Sun Microsystems, Mountain View, California), we drew regions of interest in threefold enlarged images. All the image analyses were performed blind to group membership. We outlined the temporal lobe structures with a mouse-driven cursor and then excluded the pixels that fell in the lowest 33% of the intensity range between gray matter and cerebrospinal fluid. Tissue volumes were then estimated by counting the numbers of remaining parenchymal pixels (of known size) over the slices measured. In this study, for all regions, the anterior limit was the body of the amygdala, and the posterior limit was the crus of the fornix adjoining the splenium of the corpus callosum. The hippocampus and the head size were sampled every 2 mm, and in most cases this included 12 to 15 coronal sections. The other regions, which were sampled on every other slice (4 mm), included parahippocampal gyrus, fusiform gyrus, the middle-inferior, and the superior temporal gyri. To standardize our measurements of the temporal lobe regions, we used a reference point lateral to the hippocampus, in the middle of the temporal horn, as an "anchor". From this reference point, radial lines were drawn to the deepest point of the sulci and then extended around the surface to define the relevant gyri. All data were corrected for head size. The head-size estimate, used as a surrogate for the premorbid brain size, was determined by tracing the outline of the supratentorial compartment following the dural and tentorial and midline margins. All data are calculated as the ratio of the region of interest to the head-size correction.

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