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Stimulation of the mineralocorticoid receptor improves memory in young and elderly healthy individuals

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ABSTRACT

Glucocorticoids play an important role in cognitive function and act on glucocorticoid receptors and mineralocorticoid receptors (MRs) in the brain. Previously, the blockade of the MR has been shown to impair visuospatial and working memory in healthy young men. Here, we investigated the effects of the MR agonist fludrocortisone on memory in young and elderly healthy individuals. Thirty-one young (mean age 25.4 ± 4.6 years) and 22 elderly (mean age 63.2 ± 8.2 years) healthy participants received the MR agonist fludrocortisone (0.4 mg) or placebo at least 3 days apart in a randomized, double-blind within-subject cross-over design. We measured verbal memory (auditory verbal learning test), nonverbal memory (Rey/Taylor complex figure test), and working memory (digit-span task). As expected, young participants performed significantly better than elderly individuals in visuospatial memory (effect of group: $F = 42.7$, $p < 0.01$), verbal memory ($F = 33.1$, $p < 0.01$), and working memory (digit-span backward: $F = 4.5$, $p = 0.04$). For visuospatial memory ($F = 5.0$, $p = 0.03$) and short-term and working memory (digit-span forward: $F = 4.2$, $p = 0.05$), we found a significant treatment effect indicating better memory performance after fludrocortisone compared with placebo across groups. In concert with the previous studies, our data suggest a role of the MR in memory function. A cognitive enhancing effect by MR stimulation warrants future studies.

1. Introduction

Memory function is affected by cortisol, which is released by the adrenal gland in a circadian rhythm and in response to stress (Quax et al., 2013; Schwabe et al., 2012). Cortisol exerts its effects in the brain via 2 different nuclear receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). GRs are distributed throughout the brain and have a low affinity for cortisol, whereas MRs have a high cortisol affinity and are expressed primarily in limbic areas. Both receptors are abundantly expressed in the hippocampus and prefrontal cortex, brain areas critical for verbal, visuospatial, and working memory. Lately, animal and human studies have revealed the existence of a membrane-bound, MR-mediating rapid nongenomic effects with an intermediate cortisol affinity (Henckens et al., 2011; Joels et al., 2013; van Ast et al., 2013).

Animal studies have consistently shown a role for the MR in memory performance (Joels et al., 2008). For example, blockade of MR seems to impair spatial memory (Lupien and McEwen, 1997; Qiu et al., 2010). In contrast, overexpression of MR has been consistently associated with improved memory in animals (Ferguson and Sapolsky, 2007; Lai et al., 2007). In humans, blockade of the MR impaired visuospatial, verbal, and working memory in young healthy men (Cornelisse et al., 2011; Otte et al., 2007; Rimmele et al., 2013). However, so far, no study directly examined whether MR stimulation enhances memory in healthy individuals. One recent study examined the effect of MR stimulation on sleep-dependent memory consolidation 24 hours after intake of the MR agonist fludrocortisone. Sleep-dependent memory consolidation was improved after fludrocortisone consistent with a beneficial role of MR stimulation in memory function (Groch et al., 2013).

Importantly, a particular relevance of MR activation for hippocampal memory formation has been demonstrated in aging (Yau et al., 2011). Aged mice showed impaired memory after blockade of MR but not after GR blockade (Yau et al., 2011). Furthermore, there is an evidence that MR expression in limbic areas decreases with increasing age (Berardelli et al., 2013; Choi et al., 2008; Otte et al., 2003). Aging, in turn, is associated with diminished memory function (McEwen and Morrison, 2013). However, it is not known whether a potential role of MR in memory function is depending on age.

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Table 1
Demographic variables

	Young ($n = 31$)	Elderly ($n = 22$)	p Value
Age, mean (SD)	25.4 (4.6)	63.2 (8.2)	<0.01
Sex, women/men	24/7	13/9	n.s.
BMI, mean (SD)	23.5 (4.9)	25.3 (4.9)	n.s.
Smoking, yes/no	8/22	6/16	n.s.
Years of education, mean (SD)	11.3 (1.5)	10.9 (1.8)	n.s.
BDI	2.9 (3.7)	3.1 (3.2)	n.s.

Comparison between younger and elderly participants based on 1-way analysis of variance for continuous variables and chi-square for dichotomous variables.
Key: BDI, Beck Depression Inventory; BMI, body mass index; n.s., not significant; SD, standard deviation.

Because blockade of the MR in humans impaired visuospatial, verbal, and working memory, we examined the acute effects of the MR agonist fludrocortisone on these 3 memory domains in younger and elderly healthy individuals. We hypothesized that fludrocortisone would enhance memory function in both younger and elderly individuals.

2. Methods and materials

2.1. Participants

We recruited 31 young (mean age 25.4 ± 4.6 years) and 22 elderly (mean age 63.2 ± 8.1 years) healthy participants via public posting. Criteria for exclusion were former and present *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, axis I disorders according to the mini-international neuropsychiatric interview, serious medical conditions associated with adrenal dysfunction, or well-known impact on hypothalamus-pituitary-adrenal axis activity or cognitive function, steroid use, pregnancy, and nursing. The study was approved by the local ethics committee. After complete description of the study to the subjects, written informed consent was obtained. All participants completed the study.

All participants underwent a screening procedure consisting of a medical and psychiatric history questionnaire (evaluating current lifetime psychiatric diagnosis and medical history, use of medication, alcohol, substance abuse, and smoking) and a routine medical examination. Psychopathology was further assessed with the Beck Depression Inventory and mini-international neuropsychiatric interview.

2.2. Procedures

Participants ingested 4 fludrocortisone (0.1 mg each) pills (Astonin H; Merck Serono GmbH, Germany) or 4 placebo pills looking identical in a randomized order and a double-blind crossover design with 3 days in between test days. The order of fludrocortisone and placebo administration was balanced. All subjects ingested the study medication at 2 PM. The neuropsychological assessment started at 4 PM. Blood pressure was assessed at 2 PM (baseline), 4 PM, and 5 PM by an automatic device (Carescape V100; GE Healthcare).

2.3. Neuropsychological assessment

2.3.1. Rey-Osterrieth and modified Taylor complex figure tests

These tests measure visuospatial memory. The participant is first required to copy a complex figure. Immediately thereafter (direct recall) and 20 minutes later (delayed recall), the figure has to be redrawn from memory (Hubley and Tremblay, 2002; Osterrieth, 1944).

2.3.2. Forward and backward digit-span task from the Wechsler Adult Intelligence Scale

During the forward digit-span task, participants are asked to remember a series of digits and repeat them back in the same order. During the backward digit-span task, they are asked to repeat the digits in the reverse order (Tewes, 1991).

2.3.3. Auditory verbal learning test

The auditory verbal learning test (AVLT) is a measure of short- and long-term verbal memory. The experimenter reads a list of 15 words (list A), which the participant is requested to repeat in loose order. After list A has been presented 5 times, the subject is asked to reproduce words from a newly presented distractor list (list B). After this, the subject is instructed to recall the words from list A without renewed presentation. After 30 minutes, the subject is again asked to repeat the words from list A (delayed recall). Primary outcome parameters were learning (trials 1 through 5) and delayed recall (trial 7) (Lezak, 1995).

To control for practice effects, 2 different versions of the digit-span test and the AVLT were used. For assessment of visuospatial memory, we used the Rey-Osterrieth and the modified Taylor complex figure tests, which show high correlation (Casarotti et al., 2014; Hubley and Tremblay, 2002). The order of the 2 different test days was balanced.

2.4. Statistical analyses

Demographic characteristics between younger and elderly healthy participants were compared using univariate analysis of variance (ANOVA) for continuous variables and chi-square tests for dichotomous variables. Separate repeated-measures ANOVA (rm-ANOVA) with treatment (fludrocortisone vs. placebo) as within-subject factor and group (young vs. elderly) as between-subject factor was conducted to examine differences in blood pressure and in the performance of visuospatial, verbal, and working memory.

3. Results

There were no significant differences between groups on demographic variables except age. Information on demographic variables is given in Table 1. Table 2 presents an overview of the neuropsychology results (Table 2).

To test for possible confounders, we added sex and treatment order as additional group factors; however, sex and treatment order were not associated with memory function (all $p > 0.1$) and, therefore, omitted from the analyses.

3.1. Visuospatial memory: Rey/Taylor complex figure test

Rm-ANOVA with time (copy, direct recall, and delayed recall) and treatment (fludrocortisone vs. placebo) as within-subject factors and group (young vs. elderly) as between-subject factor

Table 2
Results of neuropsychological assessment

Task	Young ($n = 31$)		Elderly ($n = 22$)	
	Placebo	Fludrocortisone	Placebo	Fludrocortisone
Rey-Taylor copy	35.5 (0.7)	35.6 (0.6)	34.7 (1.6)	35.3 (1.1)
Rey-Taylor direct	26.5 (5.2)	27.8 (4.7)	18.7 (6.3)	19.6 (4.6)
Rey-Taylor delayed	26.2 (4.9)	27.1 (4.5)	17.4 (6.5)	19.2 (4.7)
Digit-span forward	9.7 (2.0)	10.4 (1.6)	9.1 (1.9)	9.3 (1.9)
Digit-span backward	8.2 (2.3)	8.0 (2.3)	6.6 (2.6)	6.8 (2.0)
AVLT 1–5 sum score (learning)	63.4 (7.2)	63.6 (5.7)	51.8 (7.8)	54.3 (7.9)
AVLT 7 (delayed recall)	13.8 (1.5)	14.0 (1.1)	10.9 (2.1)	10.9 (2.7)

Results of assessment of visuospatial memory (Rey/Taylor complex figure test), working memory (digit-span task), and verbal memory (AVLT).
Key: AVLT, auditory verbal learning test.