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The Renin-Angiotensin-Aldosterone system in patients with depression compared to controls – a sleep endocrine study

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Abstract

Background: Hypercortisolism as a sign of hypothamamus-pituitary-adrenocortical (HPA) axis overactivity and sleep EEG changes are frequently observed in depression. Closely related to the HPA axis is the renin-angiotensin-aldosterone system (RAAS) as 1. adrenocorticotropic hormone (ACTH) is a common stimulus for cortisol and aldosterone, 2. cortisol release is suppressed by mineralocorticoid receptor (MR) agonists 3. angiotensin II (ATII) releases CRH and vasopressin from the hypothalamus. Furthermore renin and aldosterone secretion are synchronized to the rapid eyed movement (REM)-nonREM cycle.

Methods: Here we focus on the difference of sleep related activity of the RAAS between depressed patients and healthy controls. We studied the nocturnal plasma concentration of ACTH, cortisol, renin and aldosterone, and sleep EEG in 7 medication free patients with depression (1 male, 6 females, age: (mean +/-SD) 53.3 ± 14.4 yr.) and 7 age matched controls (2 males, 5 females, age: 54.7 ± 19.5 yr.). After one night of accommodation a polysomnography was performed between 23.00 h and 7.00 h. During examination nights blood samples were taken every 20 min between 23.00 h and 7.00 h. Area under the curve (AUC) for the hormones separated for the halves of the night (23.00 h to 3.00 h and 3.00 h to 7.00 h) were used for statistical analysis, with analysis of co variance being performed with age as a covariate.

Results: No differences in ACTH and renin concentrations were found. For cortisol, a trend to an increase was found in the first half of the night in patients compared to controls ($p < 0.06$). Aldosterone was largely increased in the first ($p < 0.05$) and second ($p < 0.01$) half of the night. Cross correlations between hormone concentrations revealed that in contrast to earlier findings, which included only male subjects, in our primarily female sample, renin and aldosterone secretion were not coupled and no difference between patients and controls could be found, suggesting a gender difference in RAAS regulation. No difference in conventional sleep EEG parameters were found in our sample.

Conclusion: Hyperaldosteronism could be a sensitive marker for depression. Further our findings point to an altered renal mineralocorticoid sensitivity in patients with depression.

Background

Hypercortisolism as well as a reduced feedback inhibition of the hypothalamus-pituitary-adrenocortical (HPA) system are frequently observed in depression [1–3]. Further, a decreased ability of dexamethasone to suppress adrenocorticotropic hormone (ACTH) and cortisol secretion is found in depressed patients, but appears to depend on the clinical characteristics, especially "typical" vegetative signs, as sleep disturbances and weight loss [4–8] and reproductive state in females [9].

It has been suggested that the pathophysiology of the hypercortisolism is related to a change in function of mineralocorticoid receptors (MR) (for review see [10], as a block of the MR leads to hypercortisolism in healthy controls [11,12]. However, the MR antagonist spironolacton leads to an even more pronounced activation of the HPA axis in depressed patients compared to controls [12], showing that the MR itself is functionally intact in depression.

The natural ligand of MR is aldosterone. The peripheral concentration of aldosterone is regulated by the renin-angiotensin-aldosterone system (RAAS). Several links between the regulation of RAAS and the HPA system exist. 1. ACTH is a common stimulus for cortisol, but also for aldosterone at the adrenal cortex [13]. 2. Spironolactone, an MR antagonist, increases the cortisol concentration in humans [14,15] and another MR antagonist, canrenoate, reduces the sleep related inhibition of ACTH release induced by an intravenous bolus of CRH [16]. These findings suggest an activating action of MR blockade on HPA system. The aldosterone agonist deoxicorticosterone accordingly suppresses plasma cortisol in humans [17] 3. Angiotensin II (AT II) has a direct stimulating action on CRH and vasopressin release from the hypothalamus [18,19]. 4. A polymorphism in the angiotensin converting enzyme gene seems to be related to HPA axis changes in depression [20].

What kind of change of the RAAS can be expected in depression? Several possibilities might be assumed. 1. As a consequence of the regulation of aldosterone by the HPA axis, the impact of ACTH on the secretion of aldosterone could increase, leading to a higher coupling of these hormones and a higher aldosterone concentration. 2. The activity of the RAAS and the strength of the coupling of aldosterone to renin were increased during sleep compared to wakefulness [21], i.e. it seems to be dependent on arousal. As depression is accompanied by sleep disturbances and can be viewed as a state of overarousal [22], it might be suggested that the activity of the RAAS and the strength of its coupling is weaker in depression. 3. Changes in mineral metabolism have been reported in depression [23,24]. An increase of plasma Mg^{2+} concentration seems especially to be a trade marker in patients with depression [25], plasma Na^{+} concentrations seem to be unaffected by depression [26,27], whereas plasma K^{+} has been reported to be either unaffected [27] or decreased [26]. One study showed a correlation between serum cortisol and serum Mg^{2+} [26], which points again to a close connection between the HPA-axis and the RAAS. As aldosterone leads to an excretion of Mg^{2+} [28,29], a decrease in aldosterone concentration or, alternatively, sensitivity can be assumed.

Early studies showed a reduced plasma renin activity (PRA) in depressed patients [30] and an increase in resting PRA accompanied by a blunted renin response to posture in bipolar patients [31]. The latter study described a normal aldosterone concentration, which was interpreted to be inappropriately low in relation to the increased PRA. A possible link between possible changes of the RAAS and the HPA system in depression was further demonstrated by the significant increase in aldosterone secretion after administration of the glucocorticoid receptor agonist dexamethasone in healthy female subjects, whereas in depressed females aldosterone showed a trend to a decrease [32]. The latter finding could be a hint for an increased coupling of aldosterone to ACTH in depression.

Besides endocrine changes, sleep is markedly changed in depression [33–35]. A bidirectional interaction exists between sleep and endocrine systems, especially the RAAS. Renin and aldosterone secretion increase during sleep and are synchronized to the nonREM-REM cycle [36,37]. On the other hand the aldosterone antagonist canrenoate reduced slow wave sleep (SWS) [16], whereas the MR agonist deoxicorticosterone did not influence sleep when given shortly before sleep onset [17].

In order to test the hypothesis of a decreased coupling of the RAAS and a higher impact of the HPA axis on aldosterone secretion, we examined RAAS in connection with HPA system activation and sleep EEG in depressed patients compared to controls.

Methods

Subjects

We studied nocturnal plasma concentration and sleep EEG in 7 patients with depression (1 male, 6 females, age: 53.3 ± 14.4 (mean ± SD), range 34 – 70 years) and 7 age matched controls (2 males, 5 females, age: 54.7 ± 19.5, range 27 – 76 years). The data from three of the controls were derived from the control condition of an earlier study [38] and four were newly recruited. Both patients and controls were free of medication for at least 10 days and for fluoxetine for at least 4 weeks with the exception of 1 patient receiving 500 mg chloral hydrate at the two study nights and one subject receiving metoclopramid 10

Table 1: Patients characteristics: (MDE: major depressive episode)

pat.	sex	age	diagnosis (DSM IV)	episode-duration	history	family history	sleep-disorder	appetite	mood-reagibility
1	male	57	296.32 recurrent MDE, moderate	6 month	4th episode	+	early and middle insomnia	normal	yes
2	female	38	296.33 recurrent MDE, severe, without psychotic symptoms	6 weeks	multiple episodes	-	early and middle insomnia	reduced	yes
3	female	47	296.24 MDE severe, with psychotic symptoms	6 month	2nd episode	-	early, middle and late insomnia	10 kg weight loss	no
4	female	63	296.33 recurrent MDE severe, without psychotic symptoms	6 month	3rd episode	+	none	5 kg weight loss	yes
5	female	60	296.33 recurrent MDE severe, without psychotic symptoms	6 month	multiple episodes	+	none	reduced	no
6	female	32	296.53 bipolar disorder, currently severe depression	12 month	multiple depressive episodes, one manic episode	-	hypersomnia	reduced	yes
7	female	47	296.33 recurrent MDE, severe without psychotic symptoms	6 month	several episodes	+	early and middle insomnia	10 kg weight gain	no

mg once at the day of the examination. However, even after exclusion of these subjects the main findings of the study were unchanged (data not shown). No substances for blood pressure regulation, especially beta-receptor blockers or angiotensin-converting enzyme inhibitors or diuretics were used by any of the subjects. Further no relevant co morbidity, especially no cardiovascular, renal or hepatic disorder was present in the patients or controls, as assessed by clinical examination and a standard clinical laboratory examination including serum creatinine and liver enzyme levels. The personal and family history of the controls was free of psychiatric disorders. Furthermore a major life event was also ruled out in the controls. The depressed patients were diagnosed according to DSM IV criteria. Patient did not differ in body mass index (24.6 ± 2.7 for the controls vs. 24.6 ± 4.5 for the patients, n.s.). Further characteristics are given in Table 1.

The study was approved by the Ethics committee of the University of Munich and was performed according to the Declaration of Helsinki in its version of Edinburgh, 2000. Written informed consent has been obtained from each participant before enrolment into the study.

Sleep and endocrine registration

The first study period consisted of an adaptation night, when EEG electrodes were attached without recording an EEG, followed by the examination night. For this the subjects arrived at the sleep laboratory at 19.00 h. An intravenous catheter was fixed at 19.30 h in the forearm, which was connected via a tube through the wall with the adjacent room. Therefore, it was possible to get blood samples without relevant disturbance of the subjects. The venous catheter was perfused with 0.9% saline containing 200 I.E. heparin per liter to keep the catheter patent in a constant rate of 30 ml per hour. Hormone samples were collected every 30 minutes between 20.00 h and 22.00 h and every 20 minutes between 22.00 h and 7.00 h. The first 5 ml drawn from the catheter were removed and the subsequent 10 ml used for analysis. Blood was centrifuged immediately after it was taken and the serum distributed in 3 containers, which were immediately frozen at -20°C for the rest of examination night and stored in a -80°C freezer by the next morning. The hormone analysis took place between 3 and 6 month after the examination. Only the data for the duration between 23.00 h and 7.00 h were used for analysis. The earlier data served as a control for the stress reaction by administering the catheter.

Before lights out the subjects were allowed to read or spoke with the technicians and were observed via video monitoring. After 22.00 h the subjects stayed in bed aside from rest room visits. The light was turned off at 23.00 h and the subjects were allowed to sleep until 7.00 h. At this time a polysomnography was performed.

Hormone analysis

The analysis of the serum levels cortisol, ACTH, renin and aldosterone were done by radio immunoassay with a coefficient of variation < 10 % for each hormone. The used

kits were commercial radioimmunoassays for ACTH, renin and angiotensin II provided by Nichols Institute Diagnostics, San Juan Capistrano, USA, and for aldosterone and cortisol by DRG Instruments GmbH, Marburg, Germany. All assays had a coefficient of variation of < 10 %. From the hormone concentrations the values for the area under the curve (AUC) were calculated using the trapezoid rule for the first half of the night (0 – 240 min) and the second half of the night (240 – 480 min).

Sleep EEG analysis

Sleep recordings comprised two EEGs (C3-A2, C4-A1; time constant 0.3 s, low-pass filtering 70 Hz), vertical and horizontal electrooculograms, an electromyogram, and an electrocardiogram. The electrooculogram, EEG, and electromyogram signals were filtered (EEG: high pass 0.53 Hz, -3 dB; low pass 70 Hz, -3 dB; -12 dB octave, band-stop between 42 and 62 Hz, -3 dB) and transmitted by an optical fiber system to the polygraph (Schwartzer, ED 24). Sleep EEGs were rated visually according to standard criteria [39] by an experienced rater who was blind to the study protocol. Sleep EEG parameters used for the analysis were the following: sleep onset latency [sleep onset defined as the interval between light out and the first epoch of 30 s containing stages 2, 3, 4, or REM sleep (min)]; total sleep time (min); time spent in each of the following sleep stages during time in bed (min): wake after sleep onset (WASO), stage 2, SWS (non-REM stages 3 and 4), and REM; REM latency [interval from sleep onset until the first epoch containing stage REM (min)]; REM density (rapid eye movement density, defined as the average number of 3-s mini-epochs of REM sleep including REMs per minute of REM sleep).

Statistical analysis

Statistical analysis was performed using a personal computer. The program for the statistical analysis was SPSS version 9 for Windows. Multivariate analysis of covariance was performed, taking age into account as a covariate. Because of the low number of subjects and the pilot character of this study we only present the univariate data, and have not corrected the significance level for multiple measurements. For the hormones the data were divided into the first (23.00 – 3.00 h) and second (3.00 h – 7.00 h) half of the night.

To describe possible changes in the regulatory pathways of the hormones we calculated the cross correlation between ACTH, aldosterone and cortisol as well as that of renin and aldosterone. For this analysis the "Cross correlation" function of SPSS was used. As the maximal cross correlations were generally found without time lack and no systematic shift could be observed, we only describe the results for this condition. The resulting figures represent the two tailed Pearson Correlation (see figure 1).

All values are expressed as mean ± standard deviation (SD), when not otherwise stated. A significance level of $p < 0.05$ is considered of being significant, data with $p < 0.1$ are presented and considered as trends.

Results

Depressed patients compared to controls did not show any univariate difference of the sleep EEG parameters compared to controls (Table 2). The same is true for the parameters of the first and the second half of the night (data not shown). Four of the patients and 2 of the controls had to interrupt the bed rest due to rest room visits, which took between 2.5 and 8 minutes.

Concerning endocrine parameters, for the first half of the night there was a trend to an increase in cortisol ($p < 0.06$) and a significant increase in aldosterone ($p < 0.05$), but no change in ACTH or renin secretion. In the second half of the night, a pronounced increase in aldosterone occurred ($p < 0.01$), but no significant change in the other hormones (Table 3). This endocrine change was not accompanied by changes in serum electrolyte concentrations assessed some days before the sleep-endocrine examination (mmol/l): controls (n = 5) vs. depressed patients (n = 7): Na^+: 140.6 ± 2.4 vs. 139.9 ± 2.5, (n.s.); K^+: 4.02 ± 0.08 vs. 4.04 ± 0.37, (n.s.); Mg^{2+}: 0.80 ± 0.09 vs. 0.84 ± 0.06 (n.s.).

To test the hypothesis that aldosterone release might be primarily regulated by ACTH in depression and by renin in controls, we calculated the cross correlation between the various hormone concentrations. We found high correlation coefficients between ACTH and cortisol, ACTH and aldosterone, and between aldosterone and cortisol in both depressed patients and controls. No difference between depressed patients and controls was observed (Table 4). Remarkable is the low correlation between renin and aldosterone, both in depressed patients and in controls, which suggests that during sleep ACTH is the primary trigger hormone for aldosterone in our population.

Discussion

The main new findings of this study are the huge increase in aldosterone in depressed subjects compared to controls and the unchanged cross correlation between the time course of nocturnal hormone secretion, especially between ACTH with cortisol and aldosterone and the lack of a correlation between renin and aldosterone independent of presence or absence of depression.

A difference in the regulation of aldosterone in depressed patients compared to controls has been described earlier: Aldosterone increases in response to dexamethasone in controls and shows a trend to a decrease in depressed subjects [40]. Changes in plasma renin described previously

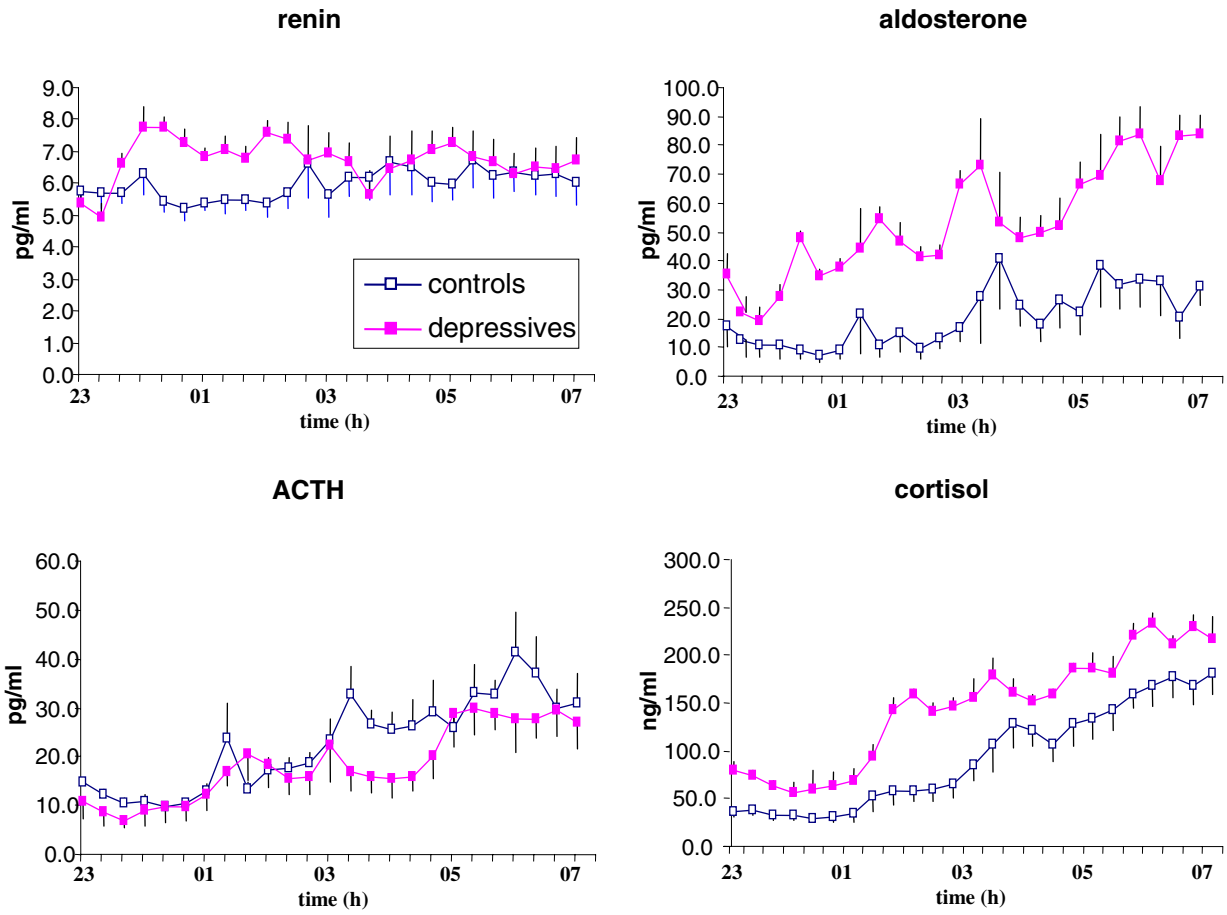

Figure 1
Time coures of nocturnal hormone secretion in patients with depression compared to controls (mean ± SEM). Cortisol is increased by trend in patients with depression compared to controls in the first half of the night (23.00 h – 3. 00 h) whereas aldosterone is significantly increased in the first and second half of the night. ACTH and renin show no difference.

Table 2: Comparison of selected sleep parameters: the parameters are based on time in bed (TIB), between controls and depressed patients (REM: rapid eye movement, REM-dens: REM-density, S2: stage 2, SOL: sleep onset latency, SWS: slow wave sleep, WASO: Wake after sleep onset).

	depressed patients	controls	significance
TIB (min)	479.2 ± 2.6	481.1 ± 4.3	n.s.
SOL (min)	15.7 ± 11.5	26.4 ± 25.0	n.s.
REM latency (min)	97.3 ± 128.0	115.4 ± 90.0	n.s.
REM dens. (min^{-1})	4.45 ± 1.66	4.46 ± 1.73	n.s.
REM (min)	92.0 ± 46.2	77.9 ± 33.3	n.s.
S2 (min)	202.6 ± 39.2	216.9 ± 59.0	n.s.
SWS (min)	17.1 ± 12.7	34.1 ± 31.3	n.s.
WASO (min)	91.4 ± 69.7	73.7 ± 79.8	n.s.

Table 3: Comparison of hormone parameters:AUC for the first (23.00 h – 3.00 h) and second (3.00 h – 7.00 h) half of the night.

	depressed patients AUC	controls AUC	significance
1. half			
ACTH (pg/ml × min)	3180 ± 1608	3193 ± 1074	n.s.
cortisol (ng/ml × min)	23690 ± 15330	11002 ± 4945	(n.s) p = 0.06
renin (pg/ml × min)	1656 ± 1000	1359 ± 249	n.s.
aldosterone (pg/ml × min)	9370 ± 5404	2914 ± 2932	p = 0.022
2. half			
ACTH (pg/ml × min)	5601 ± 1741	6807 ± 2452	n.s.
cortisol (ng/ml × min)	45682 ± 17309	33395 ± 8991	n.s.
renin (pg/ml × min)	1588 ± 919	1504 ± 433	n.s.
aldosterone (pg/ml × min)	16075 ± 5908	6799 ± 4469	p = 0.009

Table 4: Crosscorrelation between hormone concentrations (23.00 h – 7.00 h):

	depressed patients correlation coefficient	controls correlation coefficient	significance
ACTH-cortisol	0.76 ± 0.10	0.79 ± 0.18	n.s.
ACTH-aldosterone	0.65 ± 0.23	0.58 ± 0.32	n.s.
renin-aldosterone	0.07 ± 0.33	0.17 ± 0.18	n.s.
ACTH-renin	0.00 ± 0.28	0.06 ± 0.38	n.s.
renin-cortisol	-0.05 ± 0.37	0.04 ± 0.39	n.s.
aldosterone-cortisol	0.68 ± 0.29	0.63 ± 0.28	n.s.

[30] differed from our findings, possibly because of methodological differences, as we did not measure plasma renin activity but plasma renin concentration. Further, we could not find a positive cross correlation between renin and aldosterone as described earlier in healthy male subjects [37,41] and therefore could not find the expected difference in coupling of the RAAS in patients with depression compared to control.

Our data have some important limitations with regard to a general characteristic of depression. The number of patients and controls is small and consists mainly of female subjects. Typical sleep EEG changes as well as a pronounced hypercortisolism, characteristics, which have been described earlier, are missing in our populations. This might partially be due to the fact that female patients, which were the majority of our subjects, especially when premenopausal, often do not show changes classically described [9,33,42], although REM sleep changes seem to be unaffected by gender [33,43]. Therefore two possibilities arise from our findings. Firstly, the hyperaldosteronism is a more sensitive characteristic of depression compared to hypercortisolism and the classical sleep EEG findings of depressed patients, or alternatively, hyperaldosteronism is only a feature of depressed patients with certain characteristics, i.e. female gender and possibly certain psychopathological signs, as described for example in atypical depressive disorders [8,15,44]. However, we have no evidence for a high prevalence of atypical depressive features and especially not atypical vegetative features as hypersomnia and hyperphagia in our population. In fact, 5 of the patients reported a decreased appetite at the beginning of the hospitalisation. For the cross correlational data, especially for the RAAS, it might be insufficient to have measurements every 20 minutes as the sharp pulses of RAAS hormones could not be detected. This might also be an explanation for the missing cross correlation between renin and aldosterone, which has been described for controls [37]. Another explanation for this finding could also be a gender difference as the earlier studies [37,41] examined exclusively males, whereas our population consisted primarily of females. Such gender differences for the temporal pattern of secretion have been described for cortisol and growth hormone secretion [45] and can be suggested for the RAAS by findings of the influence of sex steroids and gender on its regulation [46]. Furthermore, several other factors might have influenced the results as the climatic conditions, the ambient temperature and the light conditions, which have not been specifically controlled for. As the patients and controls were examined in the same standardized sleep laboratories a major influence from these factors seems unlikely. Further

the food and fluid intake of the patients were not controlled. The controls used their normal diet. This ensured, that no adaptive changes to a standardized died occurred. As the patients were hospitalized on a psychiatric ward, a major deprivation of food and fluid can be ruled out.

Several possibilities exist for the mechanism of increased aldosterone concentration. As neither renin nor ACTH, the main releasing hormones for aldosterone, are increased other factors seem to be responsible. Two possibilities should be discussed here. 1. There is an influence of the sympathetic system which could directly interact with aldosterone secretion from the adrenal gland, although renin release is also regulated by this system via β-adrenoreceptors [47], stimulating its gene expression. Therefore, it is unlikely that changes in the sympathetic system alone contribute to the increase in aldosterone. However, the unchanged renin levels were rather unexpected, since an overactivity of sympathetic system has been shown in depressive disorder (for review see [48]). As aldosterone release is stimulated, whereas renin release is suppressed via a feedback inhibition by ATII [49], the increase in aldosterone release together with an unchanged renin level could be due to an increased ATII activity, either by an increased concentration or an increased functional activity at the receptor. Unfortunately we have not measured the concentration of ATII and therefore a level of uncertainty exists with this interpretation. Other functional systems involved in aldosterone release, which have been reported to be changed in depression include arginin vasopressin [50,51] and prostaglandins, especially prostaglandin E2 [52–54].

Despite the hyperaldosteronism no changes in electrolyte concentrations could be found in this study. The only reliable finding in the literature of a change of electrolyte levels in depression seems to be an increase in serum Mg^{2+}. As Mg^{2+} secretion is enhanced by aldosterone, these findings together with the results of the present study suggest an altered renal MR sensitivity in depression.

How this finding is related to the hypothesis of an altered MR function is unclear, especially as the recent findings by Young et al [12] question its validity. One important aspect of these experiments is the use of spironolacton as a ligand. The action of spironolacton differs from the natural ligand aldosterone, as the main metabolite of the former, canrenone, seems not to be a substrate of the multidrug resistance gene product p-glycoprotein as it passes the blood brain barrier easily [55], whereas aldosterone is hampered by this enzyme to reach the intracerebral space [56]. P-glycoprotein has recently been discussed to be involved in the neuroendocrine changes in depression [57] and the effect of antidepressant substances [54,58]. Our present data in connection to those of Young et al. [12] are in line with this hypothesis. It is further supported by the finding, that aldosterone release by human adrenal cells is increased by increased p-glycoprotein activity [59].

Conclusion

In conclusion our preliminary findings point to the possible involvement of the renin-angiotensin-aldosterone system in affective disorders. By comparing our findings with the literature a gender difference in the regulation of the RAAS is suggested. Further the data provide evidence for an altered renal MR sensitivity in depression. Finally, as hyperactivity of the RAAS is linked to altered cardiovascular regulation our findings contribute to explain the increased risk for cardiovascular diseases observed in affective disorders [60,61].

List of abbreviations

ACTH: Adrenocorticotropic hormone

ATII: angiotensin II

AUC: area under the curve

MR: mineralocorticoid receptors

PRA: plasma renin activity

REM: rapid eyed movement

RAAS: renin-angiotensin-aldosterone system

SWS: slow wave sleep

SD: standard deviation

WASO: Wake after sleep onset

Authors' contributions

HM provided the concept of the study, performed the statistical analysis, participated in the recruitment of subjects and prepared the manuscript. KH, MZ and HK participated in the recruitment of the subjects and the preparation of the manuscript. KK participated in the data management and statistical analysis. AS participated in the concept of the study and the preparation of the manuscript.

Competing interests

None declared.

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