RESEARCH ARTICLE OPEN ACCESS

A typical Realization of the process with linear recovery of Aldosterone

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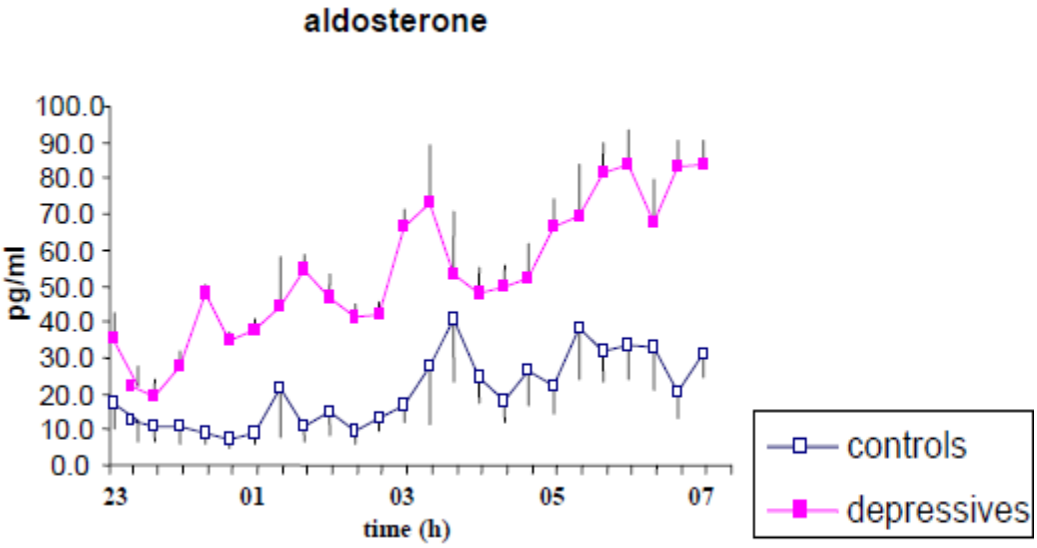
Abstract
Hypercortisolism as a sign of hypothamamus-pituitary-adrenocortical (HPA) axis overactivity and sleep EEG changes are frequently observed in depression. Closely related to the
HPA axis is the renin-angiotensin-aldosterone system (RAAS) as 1. adrenocorticotropic hormone (ACTH) is a common stimulus 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. The first passage time and the bounds of the survival functions for the application are also obtained

I. Introduction

Hypercortisolism as well as a reduced feedback inhibition of the hypothalamus-pituitary-adrenocortical (HPA) system are frequently observed in depression [1]. 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 [3] and reproductive state in females. The natural ligand of MR is aldosterone. The peripheral concentration of aldosterone is regulated by the reninangiotensin-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 . 2. Spironolactone, an MR antagonist, increases the cortisol concentration in humans and another MR antagonist, canrenoate, reduces the sleep related inhibition of ACTH release induced by an intravenous bolus of CRH . These findings suggest an activating action of MR blockade on HPA system. The aldosterone agonist deoxicorticosterone accordingly suppresses plasma cortisol in humans [2,6]. 3. Angiotensin II (AT II) has a direct stimulating action on CRH and vasopressin release from the hypothalamus. 4. A polymorphism in the angiotensin converting enzyme gene seems to be related to HPA axis changes in depression . 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 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. 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. Depressed patients compared to controls did not show any univariate difference of the sleep EEG parameters compared to controls.



Time coures of nocturnal hormone secretion in patients with depression compared to controls (mean ± SEM). aldosterone is significantly increased in the first and second half of the night.

Mathematical Model

Notations

T_n - The time interval between two consecutive stress effects.

C_n - The magnitude of aldosterone secretion due to n^{th} stress.

$N(t) = \max\{n \geq 0, \sum_{i=1}^{n} T_i \leq t\}$ be the number of stimuli.

Z - A known threshold or prespecified value of aldosterone secretion

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Realization of the process

Here the damage is allowed to decrease between successive stimuli.
That is, 'recovery' takes place in some deterministic fashion

$Z = \{Z(t), t \geq 0\}$, Such that $Z(0) = 0$ and $Z(t) \geq 0$ for all $t > 0$ with probability 1.

T_x = inf $\{t \geq 0; Z(t) > x\}$ is first passage time[4,5]. $\overline{F}(t)$ Bounds of survival function.

The survival function of T_x is

$$\overline{F}(t) = e^{-\lambda t} \sum_{k=0}^{1+[t/\alpha]} \frac{(\lambda t)^k}{k!} \left[1 - \frac{(k-1)\alpha}{t}\right]^k,$$

$t \geq 0$ …(1)

When t is large the numerical computation of (1) can be radious, because for large t, the number of terms in the sum is large. Derived the following bounds of $\overline{F}(t)$,

$$(1-\alpha/\lambda)e^{(a-\lambda)\alpha}e^{-at} \leq \overline{F}(t) \leq e^{(a-\lambda)\alpha}e^{-at} \equiv \overline{H}(t) t \leq 0,$$

where $a = -s$ and s is the largest real root of $s + \lambda = \lambda\, e^{-(s+\lambda)\alpha}$ here $\lambda = 1$ and $\alpha = 1$.

For fixed t_0, $\overline{F}(t) \leq [\overline{F}(t_0)]^k, t \geq 0$ and $kt_0 \leq t \leq (k+1)t_0, k = 0,1,2,3,...$

Therefore, upper bound of $\overline{F}(t)$ is:

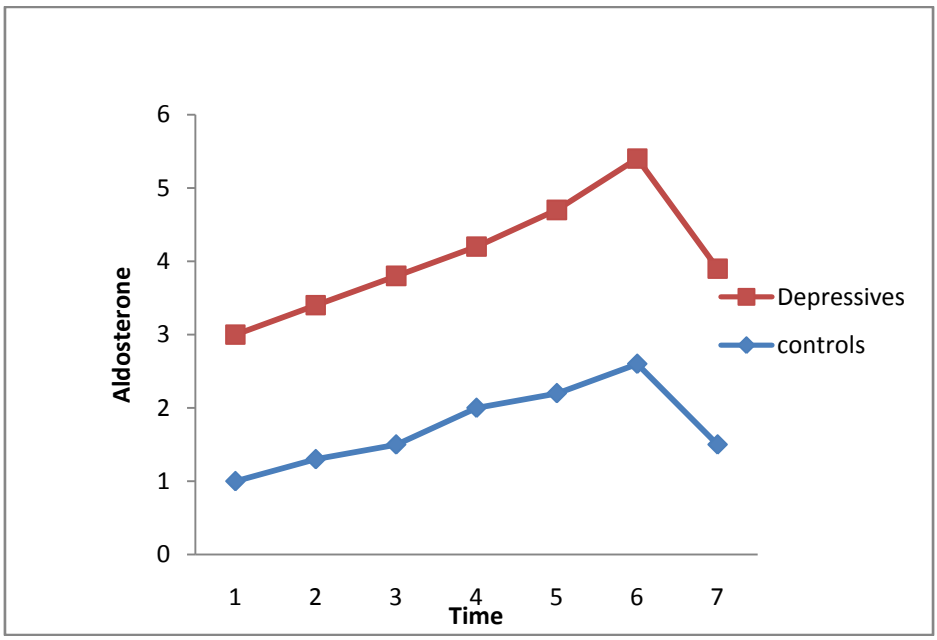
$$\overline{F}(t) \leq \min\,[\,\overline{H}\,(t), [\,\overline{F}(t_0)]^k\,]$$

When t is large enough, then

$$e^{(a-\lambda)\alpha}e^{-at} < [\overline{F}(t_0)]^k$$

The data is fitted with the distribution and the corresponding values for case:1 and case:2 are obtained as follows

Case	α	Π	t	$\overline{F}(t)$
1	0.0344	0.01 3	1 2 3 4	0.999993 0.999985 0.999972 0.999954
2	0.0464	0.0114	1 2 3 4	0.999992 0.999984 0.999975 0.999961



II. Conclusion

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 , whereas aldosterone is hampered by this enzyme to reach the intracerebral space The first passage time and the bounds of the survival functions for the application are also obtained.

References

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