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Short communication

Major depression and atrial natriuretic peptide: The role of adverse childhood experiences

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ABSTRACT

Atrial natriuretic peptide (ANP) exerts anxiolytic effects in animals and humans. Patients with anxiety, trauma-associated and depressive disorders exhibit lower ANP plasma levels compared to healthy individuals. However, the role of ANP in patients with major depressive disorder (MDD) with and without concomitant adverse childhood experiences (ACE) and in healthy individuals with and without ACE is not clear.

We recruited a total of 93 women: 23 women with MDD and ACE, 24 women with MDD without ACE, 22 women with ACE but no current or lifetime MDD, and 24 healthy women without ACE. ANP plasma levels were measured with a radioimmunoassay.

The four groups did not differ in demographic and clinical variables. We found a positive correlation between age and plasma levels of ANP ($r = .39$; $p < .001$). After controlling for age, there was no significant main effect of MDD or ACE on ANP plasma levels, but a significant interaction between MDD and ACE such that ACE was associated with reduced basal ANP levels in the absence of MDD.

We assume that low plasma ANP might be a consequence of ACE in the absence of current psychopathology. Therefore, future studies are needed to replicate our findings and to characterize the influencing factors of ACE on ANP more comprehensively, for example by including a comprehensive trauma and comorbidity anamnesis as well as cardiovascular state and risk factors.

1. Introduction

Neuroendocrine peptides have been increasingly acknowledged in psychiatric research due to their actions in the central nervous system (CNS) (Bandelow et al., 2017). Atrial natriuretic peptide (ANP) is a 28 amino acid peptide, which is synthesised in cardiomyocytes and acts in the context of blood pressure regulation. Reduced basal ANP levels have been associated with cardiovascular disease, overweight, hypertension, and insulin resistance (Wisén et al., 2011). In the CNS, ANP is expressed in the hypothalamus, brainstem, cerebellum, and cerebral cortex (Meyer and Herrmann-Lingen, 2018).

ANP contributes to hormonal feedback regulation within the two major neurobiological stress systems, i.e. the sympathetic nervous system (SNS) and hypothalamic pituitary adrenal (HPA) axis (Kellner et al., 1992; Wiedemann et al., 2000). Main target areas of ANP in the brain include the prefrontal cortex, hypothalamus, hippocampus, amygdala, and the pituitary gland (Meyer and Herrmann-Lingen, 2018). All of these brain structures have been implicated in the pathogenesis of affective and stress-related disorders. Importantly, there is evidence for anxiolytic properties of ANP in animals and humans (Wiedemann et al., 2001; Ströhle et al., 2001; Bandelow et al., 2017).

In rodents, intraventricular application of ANP was associated with anxiolytic-like behaviour (Bhattacharya et al., 1996; Meyer and Herrmann-Lingen, 2018). In an observational study of patients with risk factors for diastolic heart failure, lower MR-proANP (mid-regional pro-atrial natriuretic peptide) levels were associated with higher anxiety scores (Meyer et al., 2015). In patients with congestive heart failure, pro-ANP was negatively associated with anxiety scores (Herrmann-

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Lingen et al., 2003). In patients with panic disorder, Kellner et al. reported reduced basal ANP levels in comparison to healthy controls but no differences after administration of CRH (Kellner and Wiedemann, 1997). Administration of cholecystokinin-tetrapeptide (CCK-4), which is used for the experimental induction of panic attacks, led to a stronger increase of ANP in participants with panic disorder than in healthy controls (Wiedemann et al., 2001). This ANP elevation was in turn associated with inhibition of HPA axis activity (Wiedemann et al., 2001). Administering ANP prior to CCK-4 was associated with a reduction of induced panic attacks as well as panic severity (Wiedemann et al., 2001). These results were replicated by Ströhle et al. with a lower dosage of CCK-4 (Ströhle et al., 2001). Additionally, Kellner et al. and Seier et al. reported a stronger increase of ANP in panickers compared to nonpanickers when using lactate instead of CCK-4 (Kellner et al., 1995; Seier et al., 1997). Overall, all of these studies are consistent with anxiolytic effects of ANP.

Accordingly, in people with posttraumatic stress disorder (PTSD), Kellner et al. found reduced basal ANP levels in comparison to healthy controls (Kellner et al., 2003). However, it remains unclear, whether reduced ANP levels were associated with clinically diagnosed PTSD, if the traumatic experience was associated with changes of ANP, or if a reduction of basal ANP had been pre-existing and was a risk factor for developing PTSD after traumatic experiences.

In contrast to anxiety disorders, less is known about the role of ANP in major depressive disorder (MDD). Wisén et al. reported reduced basal ANP levels in depressed patients compared to healthy controls (Wisén et al., 2011). Krogh et al. reported an attenuated NT-proANP response to acute physical stress in depressed patients (Krogh et al., 2011). Notably, MDD is associated with a high prevalence of adverse childhood experiences (ACE), which might contribute to alterations in ANP secretion (Otte et al., 2016).

In order to better understand the role of ANP in MDD and ACE, we used a full factorial design including healthy women with and without ACE and depressed women with and without ACE. We hypothesized that MDD patients would exhibit reduced levels of ANP, which should be most pronounced in those patients with a history of ACE.

2. Methods and material

2.1. Participants

We included a total of 93 women. The sample consisted of a subgroup from a previously published study (Wingenfeld et al., 2017b), which was conducted at two study centers. Here we present data from those participants who were recruited in Berlin, as blood samples were only collected in this subgroup. Based on the structured interview, participants were assigned to four different groups: 23 women with MDD and ACE (MDD + /ACE +), 24 women with MDD without ACE (MDD + /ACE –), 22 women with ACE but no current or lifetime MDD (MDD – /ACE +), and 24 healthy women without any current or lifetime mental disorder and who did not report any form of sexual or physical abuse or abuse of any other kind (MDD – /ACE –).

2.2. Clinical assessment

All participants underwent a comprehensive clinical assessment. It included the Structured Clinical Interview for DSM-IV axis I and II capturing all psychiatric disorders from neurodevelopmental to addictive, psychotic, affective, anxiety and personality disorders among others.

Persons with MDD met clinical criteria for DSM-IV diagnosis of current major depressive episode based on SCID-I. Exclusion criteria included schizophrenia, schizoaffective and bipolar disorder, depressive episode with psychotic features, posttraumatic stress disorder, anorexia, and substance dependence. Additional depression measures included the Beck Depression Inventory (BDI-II) based on self-report and the clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS). Trait anxiety was assessed using the State-Trait Anxiety Inventory (STAI trait).

ACE was defined as repeated sexual or physical abuse at least once a month over at least one year before the age of 18 (see Heim et al., 2000b). It was assessed psychometrically by using the well-established German version of the retrospective self-rating Childhood Trauma Questionnaire (CTQ), capturing a history of adverse experiences in childhood and adolescence and sorting them into sexual, physical, and emotional abuse, as well as physical, and emotional neglect.

Healthy control subjects completed clinical interviews and self-report questionnaires in the same manner and had to be free of any current or lifetime psychiatric disorder.

Further exclusion criteria for all subjects included neurological and severe somatic (metabolic, endocrine, and autoimmune) diseases, current infections, pregnancy, and a body mass index (BMI) above 30.

2.3. Procedure

The study took place at Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin, Department of Psychiatry, Berlin. Recruiting was conducted via public postings and through the affective disorder units. All subjects provided written informed consent and received monetary remuneration (€200). The study was approved by the local ethics committee. Participants arrived at the laboratory at 8 a.m. after an overnight fast for blood collection (in supine position and after rest for the same time before starting). Blood was collected using specialized heparinized cell separation collection tubes (BD CPT™ heparin tubes, BD Biosciences). Blood was immediately frozen at -70C until laboratory analyses.

2.4. Hormonal measures

ANP concentration was determined in the neurobiological laboratory of the Department of Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf. Plasma levels of ANP were measured with a radioimmunoassay (DRG-Instruments, Marburg, Germany) after extraction. Detection limit was 0.5 pg/ml. The inter-assay coefficient of variation was < 11.6%, the intra-assay coefficient was < 8.6%. For detailed description see Kellner et al. (2003).

2.5. Data analysis

Demographic and clinical data were analyzed with ANOVAs for continuous and Chi^2 tests for categorical variables.

First, we performed a 2 (MDD +, MDD –) x 2 (ACE +, ACE –) ANCOVA with age as covariate. Age was included as covariate in all analyses because it correlated significantly with ANP. In case of significant results, we performed post-hoc t-tests. For exploratory reasons, we additionally ran correlations between ANP, MDD measures, ACE measures, anxiety measures, and demographic variables. In case of significance, we report partial η2 as effect size for ANOVA and Cohen´s d for post-hoc comparisons.

3. Results

3.1. Sample characteristics

Demographic and clinical data are shown in Table 1. The four groups did not differ significantly in age, BMI, smoking, years of education, and intake of oral contraceptives.

There was no use of psychotropic medications in the healthy women, whereas some women of the MDD + groups received antidepressant medication; there was no significant difference in medication intake between the MDD + /ACE – and the MDD + /ACE + group (35.3% with antidepressant medication). In the MDD + /ACE – group,

Table 1
Sample characteristics of subjects with MDD with and without ACE and healthy controls with and without ACE.

	MDD + /ACE + N = 23	MDD + /ACE – N = 24	MDD – /ACE + N = 22	MDD – /ACE – N = 24	statistics
Age	32.74 (10.6)	35.79 (10.4)	35.68 (11.53)	32.00 (11.2)	p = .52
Years of education	11.09 (1.5)	11.13 (1.4)	11.50 (1.3)	11.70 (1.3)	p = .42
BMI	22.45 (3.3)	22.62 (4.2)	24.07 (3.3)	21.51 (3.2)	p = .11
Smoking (Y/N)	11/12	8/16	6/16	6/19	p = .32
Intake of OC (Y/N)	7/16	8/16	5/17	7/18	p = .88
Psychotropic medication (Y/N)	6/17[a]	6/17[b]	0/22	0/25	p = .003
SNRI	2	2			
SSRI	2	2			
NDRI	2	1			
Tricyclic antidepressants	1	0			
Agomelatine	0	1			
Anticonvulsants	1	0			
Antipsychotics	0	0			
Major depression					
BDI-II	26.39 (10.6)	26.92 (8.0)	9.42 (7.1)	2.76 (3.1)	p < .001
MADRS	32.91 (6.7)	29.67 (6.6)	2.77 (2.3)	0.52 (0.9)	p < .001
Anxiety					
State-Trait Anxiety Inventory	47.52 (4.7)	48.93 (6.1)	42.05 (5.9)	41.60 (2.4)	p < .001
Adverse childhood experiences					
CTQ Sum score	62.63 (16.3)	46.13 (14.0)	65.86 (19.2)	28.33 (3.5)	p < .001

Abbreviations: MDD + /ACE + = MDD subjects with ACE, MDD + /ACE – = MDD subjects without ACE, MDD – /ACE + = subjects with ACE but no MDD, MDD – /ACE – = healthy controls, BMI = body mass index, OC = oral contraceptives, SNRI = serotonin and noradrenaline reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, NDRI = dopamine and noradrenaline reuptake inhibitor, BDI-II = Beck Depression Inventory, MADRS = Montgomery-Åsberg Depression Rating Scale, CTQ = Childhood Trauma Questionnaire.

[a] Three subjects had 2 drugs.

[b] One subject had 2 drugs.

eight subjects reported psychiatric comorbidities (two subjects with agoraphobia, one subject meeting criteria of borderline personality disorder, two subjects with persistent depressive disorder, three subjects with social anxiety disorder), and in the MDD + /ACE + group nine subjects reported psychiatric comorbidities (six subjects with persistent depressive disorder, two subjects with panic disorder, one subject with social anxiety disorder).

No subject of the MDD – /ACE + group and no healthy control (MDD – /ACE –) met DSM-IV criteria for a psychiatric disorder.

Both MDD + groups did not differ significantly in MADRS and BDI-II scores but exhibited higher scores than both MDD – groups. CTQ sum score was higher in the MDD + /ACE + group compared to the MDD + /ACE – group and healthy controls.

3.2. Atrial natriuretic peptide (ANP)

We found a significant effect of age on the plasma level of ANP (r = .39; p < .001), such that increasing age was proportionally associated with increasing plasma levels of ANP (Fig. 1a). Therefore, we included age in all further analyses. BMI, smoking, years of education, and intake of oral contraceptives did not correlate with ANP and were not included in further analyses.

2 × 2 ANCOVA with age as covariate did not reveal a significant main effect of MDD (F(1,88) < 0.01; p = .99), nor a significant main effect of ACE (F(1,88) = 1.51; p = .22) on ANP plasma levels. However, we found a significant interaction between MDD and ACE (F(1,88) = 5.99; p = .016; partial η2: .064). Post-hoc tests revealed a significant difference between the MDD – /ACE + group (M = 51.10, SD = 14.78) and the MDD – /ACE – group (M = 63.80, SD = 27.55; p = .04) (Cohen´s d = .57). In contrast, plasma levels of ANP were similar in the MDD + /ACE + group and the MDD + /ACE – group (Fig. 1b).

ANP plasma levels did not correlate with BDI-II scores (r = -0.08; p = .46), the CTQ sum score (r = -0.04; p = .72), and the STAI score (r = 0.05; p = .62).

4. Discussion

We found no main effect of MDD or ACE on plasma levels of ANP. However, there was a significant interaction between MDD and ACE, indicating that women with ACE but without current MDD had significantly reduced plasma levels of ANP compared to healthy women with neither ACE nor MDD.

The finding of reduced ANP concentrations in healthy individuals with ACE is in line with the hypothesis that ACE have long-term effects on neurobiological stress systems, such as sympathetic nervous system, the HPA axis, and the ANP system (Bandelow et al., 2017). Because ANP activity is known to dampen sympathetic and HPA activity, reduced ANP might lead to an enhanced noradrenergic and HPA axis output in traumatized individuals. Indeed, increased SNS and HPA activity has been described in traumatized individuals (Wingenfeld et al., 2015; Lu et al., 2016).

Furthermore, reduced basal ANP has been reported in patients with stress- and trauma-related disorders such as PTSD (Kellner et al., 2003). This raises the question whether reduced levels of ANP are a consequence of either a PTSD diagnosis or of traumatic experiences per se, or if reduced basal ANP levels might be a pre-existing risk factor for developing PTSD after traumatic experiences. Our findings hint to the assumption that ACE in itself is already associated with a reduction of basal plasma ANP. What remains open though is the question, whether reduced basal levels of plasma ANP are a result of ACE or if reduced levels are a pre-existing condition.

In our sample, there were no ANP alterations in individuals suffering from MDD, neither in MDD patients with ACE nor without ACE. Krogh et al. reported an attenuated NT-proANP response to exercise in depressed participants compared to healthy controls (Krogh et al., 2011). Plasma ANP during rest did not significantly differ between depressed and controls, which is in line with our results. Our findings are in contrast with another study, in which MDD was associated with reduced basal ANP (Wisén et al., 2011). However, that study did not control for ACE, PTSD, and other anxiety disorders, which might have contributed to low ANP in depressed patients. Possibly, reduced ANP in the context of ACE precipitates vulnerability specifically to anxiety

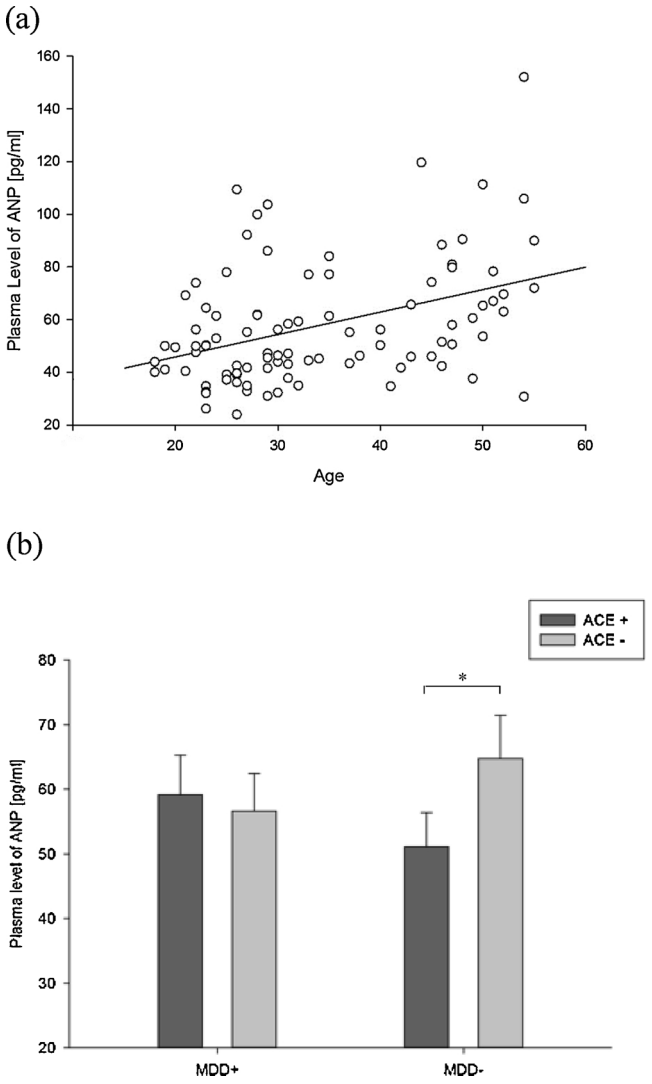

Fig. 1. a Increasing age was proportionally associated with increasing plasma levels of ANP ($r = 0.39$; $p < .001$).Figure 1b: Mean plasma levels of ANP. 2 x 2 ANOVA with age as covariate revealed no main effect of MDD or ACE, but a significant MDD by ACE interaction effect; significant post-hoc t-test: MDD – /ACE + versus MDD – /ACE –.

disorders rather than to MDD, which might explain why we did not find any alterations in the ACE group with comorbid MDD. However, we did not find a significant correlation between self-reported anxiety and plasma ANP in our sample. This is in contrast with Herrmann-Lingen et al. (Herrmann-Lingen et al., 2003), who found a negative correlation between NT-proANP and self-reported anxiety in patients with congestive heart failure. As plasma ANP is a marker of heart failure severity (Díez, 2017) and is positively associated with increasing age it is worth mentioning that we recruited a younger group (mean age was around 34 years compared to 62 years in the Herrmann-Lingen study). One could speculate, that, with increasing age, other factors influence anxiety scores and ANP levels, which are not yet manifest in younger participants. Furthermore, our sample consisted of somatic healthy patients without heart failure, which is also a major difference to the Herrmann-Lingen study.

The main strength of our study was the full factorial design with individuals suffering from MDD, ACE, or the combination of both. However, limitations have to be considered when appraising our findings. We used a cross sectional design and, therefore, cannot infer any causality. We sampled only one basal measurement of plasma ANP, which did not allow to control for the changes of plasma ANP over time. We included women only to ensure homogeneity of our sample and our results cannot be generalized to men. There was no control for menstrual cycle phase, however intake of OC did not influence our results. Finally, intake of psychotropic medication might have had an influence on ANP plasma levels as well, however, we found no difference between plasma ANP in medicated and unmedicated patients with MDD.

In sum, our results suggest that low plasma ANP might be a consequence of ACE in the absence of current depressive psychopathology. Therefore, future studies are needed to replicate our findings and to characterize the influencing factors of ACE on ANP more comprehensively, for example by including a comprehensive trauma and comorbidity anamnesis as well as cardiovascular state and risk factors.

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