Towards an improvement of the differentiation of depressive disorders. A multidimensional approach

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Anxious-retarded depression. Relations to Plasma Vasopressin and Cortisol.

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Abstract

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is related to melancholic or endogenous depression; however the strength of this relationship depends on the definition of the specific depression subcategory. A two-dimensionally defined subcategory, anxious-retarded depression is related to melancholic depression. Since arginine vasopressin (AVP) activates the HPA-axis, and both major depression and the melancholic subcategory are associated with elevated plasma AVP, we investigated whether the plasma AVP is also elevated in anxious-retarded depression, melancholic depression and anxious-retarded melancholic patients, and whether plasma AVP and cortisol are correlated in these subcategories. A total of 66 patients with major depression not using oral contraception were investigated. Patients with anxious-retarded depression had a highly significant AVP-cortisol correlation, while no such correlation was found in patients with nonanxious-retarded depression. Log-transformed mean plasma AVP values were higher in anxious-retarded than in patients with nonanxious-retarded patients. Patients with anxious-retarded melancholic also had a significantly elevated plasma AVP and a highly significant correlation between plasma AVP and cortisol levels. The correlation was low in patients with melancholic depression patients. Anxious-retarded depression may be a useful refinement of the melancholic subcategory with regard to dysregulation of the HPA-axis and plasma AVP release.

Keywords: Depression, melancholia, anxiety, retardation, vasopressin, cortisol

1 Introduction

Hyperactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis is a robust characteristic of major depression (Holsboer 1999, Scott and Dinan 1998). Basal plasma levels of cortisol and urinary excretion of cortisol are raised (Carroll et al. 1976a,b) and the secretion of corticotrope releasing hormone is increased (CRH) (Holsboer 1999, Scott and Dinan 1998). Several studies have shown that the HPA axis is dysregulated in depression. For example, the HPA axis is resistant to suppression by dexamethasone in the dexamethasone suppression test (DST) (Carroll et al. 1981), the release of adrenocorticotrope hormone (ACTH) after CRH challenge is diminished (Thalen et al. 1993), and CRH-induced release of ACTH and cortisol is increased after dexamethasone in the Dex-CRH test (Heuser et al. 1994). In, on average 30%-50% of depressed patients the HPA axis is not suppressed in the DST, with the highest rates of non-suppression being found in patients with melancholic, endogenous, familial or psychotic subcategories of depression (Nelson and Davis 1997, Rush et al. 1996). The failure to suppress the HPA axis may be cause of reduced negative feedback via glucocorticoid receptors, facilitation of CRH-induced ACTH release or both. It may be partially mediated by increased CRH release. This suggestion is supported by the finding that cerebrospinal fluid (CSF) levels of CRH are higher in patients in whom the HPA axis is suppressed in the DST (Pitts et al. 1995). Reduced CRH-dependent ACTH release has also been associated with DST non-suppressor status (Thalen et al. 1993), and has been attributed to negative feedback by high basal cortisol levels and/or down regulation of pituitary CRH receptors (Ur et al. 1992). The Dex-CRH test is a more sensitive test for detecting changes in HPA axis regulation. Depending on age and sex, 90% of depressed patients exhibit increased release of ACTH and cortisol (Heuser et al. 1994). Possible as a result of increased CRH release and reduced negative feedback by down-regulated glucocorticoid receptors (Modell et al. 1997). An increased release of CRH and reduced glucocorticoid feedback, however, cannot fully explain nonsuppression of the HPA axis or a positive Dex-CRH test. Numerous animal data obtained under physiological and pathophysiological conditions support the view that this dysregulation of the HPA axis may involve amplification of the effect of CRH by AVP (Scott and Dinan 1998). AVP produced by parvocellular and magnocellular hypothalamic neurons synergizes with CRH at the pituitary level to stimulate ACTH release (Antoni 1993). Chronic psychological stress induces a 5-fold increase of the number of AVP containing CRH neurons (de Goeij et al. 1992). Moreover, highly anxious Wistar rats and old Wistar rats have a positive response in the Dex-CRH test, which appears to depend on increased synthesis and release of AVP from parvocellular neurons of the hypothalamic paraventricular nucleus (PVN) (Hatzinger et al. 2000, Keck et al. 2002). Pathological conditions such as adrenalectomy or CRH1 receptor deficiency likewise result in an increased number of AVP containing neurons in the PVN and in the synthesis and release of AVP from the PVN, respectively (Kiss et al. 1984, Muller et al. 2000). Finally in humans CRH cannot override dexamethasone-induced suppression of the HPA axis, where as the addition of (lysine) vasopressin leads to non-suppression of the HPA axis in the DST, like that seen in depressed patients (Von Bardeleben et al. 1985).

Thus AVP has become a peptide of major interest in depression research and may be specifically involved in the hyperactivity of the HPA axis in certain subcategories of major depression. In support of this hypothesis, plasma AVP levels are elevated in patients with major depression and in patients with the melancholic subcategory compared with healthy control subjects (Van Londen et al. 1997). Moreover, plasma AVP and cortisol levels are positively correlated in depressed patients (Inder et al. 1997a). Interestingly, plasma AVP levels are higher in hypercortisolemic depressed patients than in patients with normal cortisol levels and healthy controls (Inder et al. 1997a). The finding that CSF AVP is non-significantly elevated in patients in whom the HPA axis is not suppressed in the DST (Pitts et al. 1995) suggests that AVP release may be increased in these individuals.

These data suggest that increased AVP release is related to a specific subcategory of depression in which the HPA axis is not suppressed during the DST, rather than to depression in which responses are increased in the Dex-CRH test.

Investigations of DST non-suppression in subcategories of major depression have shown that the strength of the relationship between non-suppression and endogenous or melancholic subcategory depends on the definition used. The nonsuppression rate is lower if the endogenous or melancholic subcategory is defined according to the Diagnostic and Statistical Manual for Mental Disorders (DSM)-III (American Psychiatric Association 1980) or DSM-IV (American Psychiatric Association 1994) than if melancholic depression is defined according to Research Diagnostic Criteria (RDC) or Newcastle criteria (Rush and Weissenburger 1994). In another study, we found that anxious-retarded depression had a significant overlap with melancholic depression according to the DSM-IV (De Winter et al. 2004). The definition of anxious-retarded depression was based on median scores for two dimensions anxiety and retardation, and appeared to be associated with a family history of depression (De Winter et al., 2004). Since plasma AVP levels are raises in major depression and melancholic depression (Van Londen et al. 1997), the present study primarily investigated whether plasma AVP levels are raised in anxious-retarded depression. Since plasma AVP and cortisol levels are correlated (Inder et al. 1997) we also investigated whether this is the case for anxious-retarded depression. Patients with non-anxious-retarded were used as control subjects. We also measured plasma AVP and cortisol levels, and their correlation, in patients with melancholic depression (DSM-IV) and in patients with non-melancholic depression, hypothesizing that elevated plasma AVP levels and a positive correlation between AVP and cortisol levels would be found in the melancholic patients. We further explored whether the relation between plasma AVP and anxious-retarded depression was due to a relation between plasma AVP and melancholic depression or vice versa. We therefore compared the AVP levels and AVP-cortisol correlations in patients with anxious-retarded melancholic depression and in the category of all other depressed patients.

2 Methods

2.1 Subjects

A total of 81 patients with major depression recently admitted to the in- and out-patient university clinic of the Rijngeest Groep were recruited for a 2-year cross-sectional, prospective follow-up study of the role of stress hormones in the outcome of depression. All patients were referred to the study by the psychiatrist who made the initial diagnosis of major depression. After confirmation of the diagnosis by RFPdeW, using a semi-standardized interview, the patient was asked to participate in the study. Written informed consent was obtained for all patients, and the Ethical Committee of Leiden University Medical Center (LUMC) approved the informed consent protocol.

Patients were included if they fulfilled DSM-IV criteria for major depressive episode (American Psychiatric Association 1994) and scored at least 21 on the Montgomery Åsberg Depression Rating scale (MADRS) (Montgomery and Asberg 1979). Exclusion criteria were bipolar disorder, treatment with lithium, carbamazepine or valproate; first episode of major depression at or above the age of 60 years; alcohol or drug abuse or dependence; pregnancy; or clinical evidence of a medical illness that could be associated with abnormal plasma AVP release, such as the syndrome of Inappropriate Secretion of Anti Diuretic Hormone.

Because short term drug withdrawal may influence the regulation of the HPA axis (Kraus and Grof 1985), and we considered long term withdrawal to be not feasible as it may lead to a high drop-out rate among patients with severe depression, patients continued to

take their prescribed medication during the investigation. In exploratory analyses we confirmed that oral contraceptives decrease plasma vasopressin levels (Ekstrom et al. 1992) (Kostoglou-Athanassiou et al. 1998), and increase plasma cortisol levels (Amin et al. 1980). Therefore, 15 patients taking oral contraceptives were excluded, as were patients with depression in relation to panic disorder not included, since they participated in a different research project.

2.2 *Demographic, clinical and treatment characteristics*

Of the 66 depressed patients with a mean age of 41 years (SD 11.7), 59% were female, 53% had a positive family history, and 56% were outpatients (n = 37). The mean number of previous episodes was 1.59 (SD 1.95). A total of 29 experienced their first episode of major depression. The average duration of the current episode was 6.8 (SD 7.0) months. A total of 31 patients smoked more then one cigarette a day. Altogether 45 patients did not use alcohol, 20 patients consumed one to three alcoholic beverages daily, and one patient consumed maximally four alcoholic beverages daily in the month before the investigation. Alcohol consumption was thus lower than that associated with an increased risk of depression (5 consumptions) (Wang and Patten 2001). All patients refrained from using alcohol for 12 h before the investigation.

Of the 66 patients, nine used a neuroleptic drug, 39 an antidepressant drug,16 a selective serotonin reuptake inhibitor, 15 a serotonergic and noradrenergic reuptake inhibitor, and 8 a tricyclic drug) and 38 a benzodiazepine. For correlational studies currently accepted equivalent values of the dosages were computed (Moleman and Birkenhaeger 1998). Of the patients on antidepressant treatment, five additionally used a neuroleptic plus a benzodiazepine, two a neuroleptic, and 20 a benzodiazepine. Two psychotically depressed patients used only an antipsychotic drug and 13 patients used only a benzodiazepine

2.3 *Assessments*

2.3.1 *Psychopathology*

RFPdeW performed the psychopathological assessments using a semi-standardized interview. This interview encompassed the DSM-IV criteria for depressive disorder, subcategorisation of DSM-IV melancholic depression, and the Comprehensive Psychopathological Rating Scale (CPRS) (Asberg et al. 1978; Goekoop et al. 1992). The CPRS is a widely used scale for the assessment of psychopathological signs and symptoms. The inter-rater reliability is comparable with that of the Present State Examination (Goekoop et al. 1991), and factor-analysis in a heterogeneous patient sample has shown that its 65 items may be reduced to five global factors of psychopathology, one of which is a bipolar component (Goekoop et al. 1992). Three of these 5 components represent non-psychotic psychopathology. They are called emotional dysregulation, motivational dysregulation (the bipolar component comprising 2 dimensions of inhibited and disinhibited motivational dysregulation, respectively) and autonomic dysregulation. The 2 psychotic dimensions are called perceptual disintegration and behavioral disintegration (Goekoop et al. 1992). All 6 dimensions conform to the Rasch model (Goekoop and Zwinderman 1994) and confirmatory factor analysis has shown that all dimensions except behavioral disintegration are confirmed in the domain of unipolar major depression (Goekoop et al. unpublished data).

Since we were specifically interested in the major differentiation of unipolar depression, we used three non-psychotic dimensions: Emotional dysregulation, motivational inhibition and autonomic dysregulation. Emotional dysregulation comprises *general neurotic* signs and symptoms of inner tension, concentration difficulties, reported sadness, pessimistic thoughts, reduced sexual interest, inability to feel, reduced sleep,

indecision, apparent sadness, fatigability, failing memory, lassitude, reported muscular tension, reduced appetite, phobias, suicidal thoughts, worrying over trifles, compulsive thoughts, depersonalization and derealization. Motivational inhibition comprises the signs and symptoms related to psychomotor retardation apparent sadness, inability to feel (particularly anhedonia), slowness of movement, reduced speech, and inappropriate emotional expression (including affective flattening). Autonomic dysregulation comprises signs and symptoms of predominantly somatic anxiety, such as inner tension, reported autonomic symptoms, observed muscle tension, reduced sleep, aches and pains, and observed autonomic symptoms. Correlational analysis has shown that the major differentiation of depressive disorders is due to autonomic dysregulation ('anxiety') and motivational inhibition ('retardation'), while emotional dysregulation is a more general dimension (Goekoop et al. unpublished data). We therefore used the former two dimensions for the present study. To make four two-dimensionally defined subcategories of depression we used dichotomous ratings based on median scores for the dimensions autonomic dysregulation ('anxiety') and motivational inhibition ('retardation'). These subcategories were called anxious-retarded, (non-retarded) anxious, retarded (non-anxious) and undifferentiated depression. The anxious-retarded subcategory was selected for the present study because of its high association with the melancholic subcategory (Goekoop et al. unpublished data, see also Results).

2.3.2 Biochemical assay procedures

Within 7 days after the CPRS interview blood samples were drawn on a single day under standardized rest conditions between 09.00h and 9.30h and between 15.30h and 16.00h. All patients refrained from the use of alcohol and abnormal motor activity (sports) during the 12-h period preceding the study. They were seated 15 minutes before venipuncture, and smoking was prohibited during 30 minutes preceding the venipuncture. Eating and drinking were ad libitum.

Blood was sampled by venipuncture in 10-ml vacutainer tubes and immediately stored at 4 °C. Within 30 minutes plasma was separated and stored at -80 °C until AVP and cortisol analysis. Plasma AVP was determined by radio-immuno-assay (RIA), and total plasma cortisol was measured by high performance liquid chromatography (HPLC) with UV detection as previously described (Van Londen et al. 1997). For plasma AVP the detection limit was 0.5pg/ml for plasma (extracted assay), and the intra-and interassay coefficients of variation were 9.9% and 15.9%, respectively. For cortisol the detection limit was 0.01 mg/l and the intra-assay coefficient of variation was 2.9 %. In the present study plasma osmolality was not assessed since in our previous study of depressed patients no association had been found with plasma AVP (Van Londen et al. 1997).

2.4 Statistical analyses

The association between anxious-retarded depression and melancholia was quantified by Cohen's kappa. Plasma AVP and cortisol levels were calculated as the average of the morning and afternoon values. Plasma AVP values were not normally distributed. Therefore differences between subcategories were analyzed by Mann-Whitney U tests and correlations with plasma cortisol and psychotropic drug dosage were analyzed with Spearman's rank correlations. For multivariate analysis, plasma AVP values were log-transformed into ln(AVP). Differences in ln(AVP) and cortisol between anxious-retarded and non-anxious-retarded, melancholic and non-melancholic, as well as anxious-retarded melancholic and all other patients were analyzed with Students' t tests. Pearson's correlations were used for the correlations between ln(AVP) and cortisol. The effects of medication, age (dichotomized as older or younger than the median of 42 years, as well as older or younger than the menopausal age of 50 years) and sex on ln(AVP) were investigated by analysis of variance (ANOVA). The effects of these parameters on the correlation between ln(AVP) and cortisol were analyzed by ANOVA using ln(AVP) as the

dependent variable and cortisol as the covariate. The association between ln(AVP) and anxious-retarded depression or melancholic depression was also investigated by ANOVA. All calculations were carried out using SPSS 9.0 (SPSS INC, Chicago)

3 Results

Relation between anxious-retarded depression and melancholic depression
In all, 25 patients had anxious-retarded depression and 34 had melancholic depression. Totally, 22 patients (88% of the patients with anxious-retarded depression and 65% of the patients with melancholic depression) fulfilled the criteria for both subcategories. The correspondence between the anxious-retarded and melancholic subcategories was 0.549 (Cohen's kappa, $p < 0.001$).

3.1 Plasma AVP and Cortisol in major depression

Mean values, and effects of drug treatment, age and sex
Table 1 shows plasma AVP and cortisol levels and AVP-cortisol correlations in patients with different subcategories of major depression. The mean plasma AVP concentration was 4.5 pg/ml (S.D. 4.87). In subgroups of patients on different medications, Spearman's correlations between drug dosage and plasma AVP were 0.267 for the SSRI subgroup ($n = 16$, $p = 0.317$), -0.231 for the SNRI subgroup ($n = 15$, $p = 0.408$), -0.771 for the TCA group ($n = 8$, $p = 0.025$), 0.124 for the antipsychotic subgroup ($n = 9$, $p = 0.750$) and -0.162 for the benzodiazepine subgroup ($n = 38$, $p = 0.333$). ANOVA showed that in the whole group, treatment with SSRI, SNRI, TCA, antipsychotic drug or benzodiazepine was not related to ln(AVP). F values (p values between brackets) related to these drug treatments were 0.134 (p=0.715), 0.007 (p=0.935), 0.818 (p=0.369), 0.069 (p=0.794) and 0.105 (p=0.747) respectively. Likewise ln(AVP) did not depend on the dosage of these psychotropic drugs. F values (*p* values between brackets) were 0.682 (p=0.412), 0.330 (p=0.568), 0.532 (p=0.468), 2.263 ($p = 0.138$) and 0.171 (p=0.680), respectively finally there was no interaction between antidepressants and antipsychotics, antidepressants and benzodiazepines, and antipsychotics and benzodiazepines. F values were 0.554 (p=0.460), 0.468 (p=0.497) and 0.445 (p=0.507), respectively. Neither age (< or ≥ 42 years) nor sex, nor their interaction, were related to ln(AVP). F values were 0.011 (p=0.918), 0.348 (p=0.557) and 0.238 (p=0.628), respectively. If a menopausal age criterion of 50 years was used, then the F values were 2.349 (p=0.130), 0.165 (p=0.686) and 0.003 (p=0.957), respectively.

Table 1
Plasma AVP and Cortisol with standard deviation (SD) and Spearman correlations between plasma AVP and Cortisol for all patients, as well as for anxious-retarded versus non-anxious-retarded, and melancholic versus non-melancholic patients.

(Sub)categories	n	AVP pg/ml		Cortisol mg/ml		AVP-Cortisol	
		Mean	SD	Mean	SD	Correlation	p
Major depression	66	4.50	(4.87)	145.4	(41.2)	.35	0.005
Anxious-retarded	25	6.25[a]	(7.06)	148.6	(44.6)	.56	0.004
Non-anxious-retarded	41	3.44[a]	(2.38)	143.4	(39.5)	.24	0.126
Melancholic	34	5.50	(6.22)	148.5	(41.4)	.39	0.024
Non-melancholic	32	3.44	(2.53)	142.1	(42.4)	.27	0.133
Anxious retarded melancholic	22	6.75[b]	(7.39)	148.6	(47.3)	.59	0.004
All other patients	44	3.38[b]	(2.31)	143.8	(38.4)	.25	0.098

Differences between means (Mann Whitney) [a]: p=0.09; [b]: p=0.046

The mean plasma cortisol concentration was 145.4 mg/ml (41.2). In subgroups of patients on different medications, Spearman's correlations between drug dosage and plasma cortisol were 0.302 for the SSRI subgroup (*n* = 16, p = 0.255), -0.011 for the SNRI subgroup (*n* = 15, p = 0.969), 0.072 for the TCA group (*n* = 8, p = 0.691), 0.080 for the antipsychotic subgroup (*n* = 9, p = 0.838) and -0.126 for the benzodiazepine subgroup (*n* = 38, p = 0.451).

Treatment with SSRI, SNRI, TCA, antipsychotic drug or benzodiazepine was not related to plasma cortisol concentration. F values (p values between brackets) related to these drug treatments were 0.222 (p=0.639), 0.347 (p=0.558), 1.129 (p=0.292), 1.133 (p=0.291) and 0.108 (p=0.743) respectively. Similarly, plasma cortisol concentration was not associated with psychotropic drugs dosage. F values (p values between brackets) were 0.119 (p=0.732), 0.022 (p=0.881), 0.442 (p=0.508), 1.439 (p=0.227) and 0.149 (p=0.701) respectively. Interaction effects were analyzed for antidepressants and antipsychotics, antidepressants and benzodiazepines, and antipsychotics and benzodiazepines. F values were 0.596 (p=0.443), 1.439 (p=0.235) and 0.956 (p=0.332), respectively. Neither age (< or ≥ 42 years) nor sex, nor their interaction, were related to ln(AVP). F values were 0.013 (p=0.908), 0.020 (p=0.999) and 0.013 (p=0.909), respectively. If the menopausal age criterion of 50 years was used, then the F values were 1.799 (p=0.185), 0.040 (p=0.841) and 0.062 (p=0.804), respectively

3.2 Correlations between plasma AVP and cortisol, and effects of drug treatment, age and sex

A statistically significant positive correlation (Spearman's r= 0.35, p=0.005) was found between plasma AVP and cortisol for all 66 patients with major depression. After logarithmic transformation of AVP concentrations the Pearson's correlation was 0.37 (p=0.002). ANOVA further showed that neither medication with SSRI, SNRI, TCA, antipsychotic drug and benzodiazepine nor the above mentioned interactions of drug treatments were related to the correlation between ln(AVP) and plasma cortisol, the significance of the association being only slightly reduced (p=0.004) after correction for these factors. ANOVA of age (< or ≥ 42 years), sex and their interaction and cortisol as covariate of ln(AVP) showed that the significance of the covariation between cortisol and

ln(AVP) in depression again was only slightly reduced (p=0.003). If the menopausal age criterion of 50 years was used, then the significance of the covariation was again slightly reduced (*p* = 0.005).

3.3 Plasma AVP and Cortisol in patients with anxious-retarded depression, melancholic depression or anxious-retarded melancholic depression

Differences between mean values, and effects of drug treatment, age and sex. Patients with anxious-retarded patients had a higher plasma AVP concentration than patients with non-anxious-retarded patients (Mann-Whitney U test, p= 0.09, two-tailed). After logarithmic transformation of AVP concentrations the difference was statistically significant (t test: p=0.031, two-tailed). The difference in plasma AVP or ln(AVP) between patients with melancholic or non-melancholic depression was not significant, (p= 0.090, Mann Whitney, and 0.130, t-test, respectively). Patients with anxious-retarded melancholic depression had a significantly higher plasma AVP and ln(AVP) than all other patients (p = 0.046 and 0.013 respectively). ANOVA showed that the dosage of SSRI, SNRI, TCA, antipsychotic drug and benzodiazepine did not have a confounding effect on the relation between ln(AVP) and anxious-retarded depression. F values (p values between brackets) were 1.787 (p=0.386), 1.778 (p=0.198), 0.680 (p=0.420), 1.855 (p=0.189) and 0.026 (p=0.874) respectively. Similarly, dosage of SSRI, SNRI, TCA, antipsychotic or benzodiazepine did not affect the relation between plasma cortisol level and anxious-retarded depression. F values (p values between brackets) were 0.005 (p=0.945), 1.279 (p=0.272), 1.136 (p=0.300), 0.252 (p=0.621) and 0.738 (p=0.401) respectively.

ANOVA showed that age (< or ≥ 42 years), sex and their interaction did not have a confounding effect on the relation between ln(AVP) and anxious-retarded depression, melancholic depression or anxious-retarded melancholic depression. F values (p values between brackets) related to age, sex and their interaction were 0.707 (p=0.410), 0.011 (p=0.916) and 1.265 (p= .0273) for the anxious retarded subcategory, 0.109 (p=0.743), 0.562 (p=0.459) and 0.555 (p=0.462) for the melancholic subcategory, and 0.001 (p=0.975), 0357 (p=0.558) and 2.554 (p=0.127) for the anxious-retarded melancholic depression. ANOVA with anxious-retarded depression and melancholic depression as independent variables showed that ln(AVP) was only associated with the anxious-retarded subcategory of depression (p=0.031). There was no association between cortisol level and subcategory of depression.

3.4 Correlations between plasma AVP and cortisol, and effects of age and sex

In patients with anxious-retarded depression, Spearman's correlations between plasma AVP and cortisol were 0.56 (n= 25; p=0.004) and 0.24 (n=41; n.s.), respectively. In patients with melancholic or non-melancholic depression, these correlations were 0.39 (n=34; p=0.024) and 0.27 (n= 32; n.s.), respectively. The correlation between plasma AVP and cortisol levels in the 22 patients with anxious-retarded melancholic depression was0.59 (p=0.004), while in the 44 other patients it was 0.253 (p=0.098). After logarithmic transformation of AVP concentrations, the Pearson's correlations between ln(AVP) and plasma cortisol were 0.61 (p=0.001) and 0.17 (p=0.302) for patients with anxious-retarded or non-anxious-retarded patients, 0.43 (p=0.011) and 0.27 (p=0.141) for patients with melancholic or non-melancholic depression, and 0.63 (p=0.002) and 0.16 (p=0.289) for patients with anxious-retarded melancholic patients and all other patients. After correction for age (< or ≥ 42 years), sex and their interaction, ANOVA with concentration as covariate revealed a slightly lower association between cortisol concentration and ln(AVP) in anxious-retarded patients (p=0.005), melancholic depression (p= 0.017) or anxious-retarded melancholic depression (p=0.004).

4 Discussion

We replicated the finding that major depression is associated with a positive correlation between plasma AVP and cortisol (Inder et al. 1997). This correlation was due to a highly significant correlation between plasma AVP and cortisol in patients with anxious-retarded depression. We also showed that this anxious-retarded subcategory of depression was associated with a higher of plasma AVP level than the complementary non-anxious-retarded subgroup, but it was only significant when logarithmic-transformed AVP values were used.

In patients with melancholic depression (65% of the patients had anxious-retarded depression), there was a low correlation between plasma AVP and cortisol. These patients had a non-significantly higher plasma level of AVP than the patients with non-melancholic depression. Like the patients with anxious-retarded depression, the patients with anxious-retarded melancholic depression (88% of the patients with anxious-retarded depression) had a significantly higher plasma AVP level and a highly significant AVP-cortisol correlation. This suggests that anxious-retarded depression may be a two-dimensional refinement of the melancholic subcategory and a more useful clinical phenotype than the melancholic subcategory as far as external validity involving plasma AVP related HPA-axis dysregulation is concerned.

The increased plasma AVP level combined with the correlation between plasma AVP and cortisol levels in the patients with anxious-retarded depression is the third report supporting the hypothesis that AVP is involved in the dysregulation of the HPA-axis in depression. As already mentioned, one study demonstrated a correlation between plasma AVP and cortisol in major depression (Inder et al. 1997), and another study showed that the number of CRH neurons coexpressing AVP in the PVN of the hypothalamus was almost three times higher than in a control group (Raadsheer et al. 1994). However, in an earlier study (Van Londen et al. 1997), we found no correlation between plasma AVP and cortisol levels. The reason for this difference is unclear. Whether drug withdrawal may have played a role will have to be investigated. The previously reported statistically significant elevation of plasma AVP in melancholic depression (Van Londen et al. 1997) was not reproduced in the present study. This may be because this relationship was only found for plasma AVP levels at 23.00, a time not assessed in the present study. Another reason is that DSM-III-R criteria for melancholic depression were used in our previous study.

The specific phenotypic characteristic of patients with high plasma AVP and high AVP-cortisol correlation appears to be the combination of both high anxiety and high retardation. This differentiates these patients from highly anxious or highly retarded patients, as well as from highly anxious, low-retarded patients and highly retarded low-anxious patients. The combination of high anxiety, high retardation, and high plasma AVP with positive AVP–cortisol correlation suggests a common pathogenetic pathway that involves disinhibition of the HPA-axis as well as disinhibition of the two coping systems for fight/flight and behavioral inhibition (Bohus and Koolhaas 1993). Since these two systems centrally involve CRH and AVP neurotransmission, respectively, reduced negative feedback or increased release of both CRH and AVP may occur in the anxious-retarded subcategory of depression. This could be due to reduced hippocampal and/or hypothalamic glucocorticoid feedback function (Sapolsky and Plotsky 1990,Kovacs et al. 2000) and/or to enhanced noradrenergic activation (Scott and Dinan 1998). Although it is generally accepted that peripheral plasma AVP levels reflect osmotic regulation activity of the magnocellular neurosecretory system, the elevated plasma AVP in the anxious-retarded depression could be because of a disinhibited response to psychological stress. In this case the response could originate in the parvocellular neurons in the hypothalamic

PVN and reach the pituitary via the portal circulation, as indicated by the results of animal studies of 'psychological' stress (Keck et al. 2002, Scott and Dinan 1998). The higher correlation between plasma AVP and cortisol may be because of synergy between AVP derived from the parvocellular PVN and CRH at the level of the pituitary. However, increased plasma AVP levels may also directly stimulate adrenocortical glucocorticoid secretion (Guillon et al. 1995). Altough we have no evidence for this from this study. Increased plasma AVP levels could also originate from the magnocellular system. The lack of a correlation between plasma AVP levels and plasma osmolality in our earlier study (Van Londen et al. 1997), makes the latter explanation unlikely.

Psychotropic agents may have confounded the association between plasma AVP levels, or the correlation between plasma AVP and plasma cortisol levels and anxious-retarded depression, because the SSRI fluoxetine has been shown to reduce hypothalamic AVP release *in vitro* (Altemus et al. 1992) and in some studies antipsychotic drugs have been shown to influence plasma cortisol and AVP levels (Gattaz et al. 1995, Raskind et al. 1987). In these 66 patients with major depression, we only found a negative correlation between TCA dosage and plasma AVP level in the whole group of depressed patients. This finding was no longer significant after correction for multiple assessments. To detect the effects of treatment on plasma AVP levels, it may be better to measure plasma AVP levels of those drugs whose antidepressant is known to be related to their plasma concentration. The finding that neither age (< 42 or ≥ 42 years; < 50 or ≥ 50 years) sex, nor their interaction explained the elevated plasma AVP levels in patients with anxious-retarded depression, and that no difference was found between young men and women, suggests that postmenopausal nor perimenstrual effects did not confound the data.

We found that the mean plasma AVP level was 4.5 pg/ml, which may seem rather high compared to data reported by others. Our healthy control group of 17 subjects, however, had a mean plasma AVP level of 3.17 pg/ml (range 1.20 –9.11pg/ml; SD 1.97), which is similar to previously reported concentrations (ranging from 1.2 pg/ml ± 0.6 to 3.5 ± 0.6 pg/ml) measured by RIA plasma extraction (Glanzer et al. 1984, Viinamaki et al. 1986) . This suggests that it is unlikely that the RIA method used resulted in systematically higher plasma AVP values, and that the high mean plasma AVP level in this depressed patient group was due to a subgroup with extraordinary high levels (the anxious-retarded depression subgroup).

In conclusion, anxious-retarded depression, which has been related to family history, appeared to be a phenotypic subcategory showing a correlation with high plasma AVP levels and a high AVP-cortisol correlation. Anxious-retarded depression was significantly associated with melancholia and patients with anxious-retarded melancholic depression also had high plasma AVP levels and a high correlation between plasma AVP and cortisol levels. These findings suggest that this two-dimensional refinement of the melancholic subcategory of depression may be useful for further investigations of plasma AVP-related dysregulation of the HPA axis in familial depression.

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