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

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Reduced cooperativeness and reward-dependence in depression with above-normal plasma vasopressin concentration.

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Journal of Psychopharmacology 2008 Jun 26. [Epub ahead of print]

Abstract

The neuropeptide vasopressin is centrally involved in the regulation of social behaviour and response to stress. We previously found support for a subcategory of depression defined by above-normal plasma vasopressin (AVP) concentration. This subcategory is validated by a positive family history of depression and correlating plasma AVP and cortisol concentrations. The data support the validity of above-normal plasma AVP concentration as a genetically determined biological marker for a subcategory of depression. The aim of the present study was to test whether above-normal plasma AVP concentration in depression is related to personality characteristics reflecting a specific social behaviour style.

The data of 78 patients from a previously investigated sample were reanalysed. Fifty-eight patients were available after 2 years, 15 of whom with initially above-normal plasma AVP. The dimensions of the Temperament and Character Inventory (TCI) were scored, with particular focus on the dimensions of Cooperativeness (CO) and Reward-dependence (RD). Normative subjects and other depressed subjects were used as controls. After full remission, patients with initially above-normal AVP had low CO compared with normal and patient controls. During depression, these patients had both low CO and low RD compared with normal controls and low RD compared with patient controls. Low CO is a presumably premorbid trait and reduced RD a state-dependent characteristic in depression with above-normal plasma AVP. The low CO further supports the validity of above-normal plasma AVP concentration as a genetically determined biological marker for a subcategory of depression.

Keywords: Depression, personality, dimensions, socialization, vasopressin

1 Introduction

This study is a part of a series of investigations, in the same patient sample that aims to detect biological markers of diagnostic subclasses of depression with higher validity than the current subclasses of the Diagnostic and Statistical Manual IV (DSM-IV; American Psychiatric Association, 1994). We assumed that higher validity of depressive subcategories could be achieved by multi-dimensional description of clinical pictures using global dimensions of psychopathology (Goekoop et al. 1992), relations with a positive family history of depression, and multi-dimensionally defined personality profiles using the dimensions of the Temperament and Character Inventory (TCI) (Cloninger et al. 1993).

Because depression is conceived as a disorder of the response to stress and vasopressin (AVP) plays a major role in the response to severe stress conditions (Antoni 1993), the biological markers of depressive subcategories were sought at the level of vasopressinergic activation of the hypothalamus–pituitary–adrenal (HPA)-axis. Because AVP is also centrally involved in the regulation of social behaviour (Young 2002), genetically deficient vasopressinergic mechanisms could play a role in both the premorbid personality and the pathophysiology of subcategories of depressive disorders.

At the vasopressinergic level of analysis, we used the following parameters: a high correlation between plasma AVP and cortisol concentrations, which could be a parameter of increased responsivity of the pituitary vasopressin-1b (V1b) receptor, as it has been found after severe stress (Volpi et al.2004), and above-normal plasma AVP concentration, which, because of its relation with familial depression (Goekoop et al. 2006), could be a parameter of genetically increased AVP synthesis and/or release, as it has been found in highlyanxious inbred rats (Murgatroyd et al. 2004).

Up to now, we found support for two better-validated subcategories of depression than the melancholic subtype according to the DSM-IV: a highly anxious-retarded subcategory (De Winter et al. 2004) and a subcategory defined by above-normal plasma AVP concentration (Goekoop et al. 2006). Both subcategories showed a correlation between plasma AVP and cortisol (De Winter et al. 2003, Goekoop et al. 2006). The highly anxious-retarded subcategory was further related to melancholia (De Winter et al. 2004) and was characterized by poor long-term outcome (De Winter et al. 2006), familial depression (De Winter et al. 2004) and a low score on the dimension of self-directedness (SD) of the TCI after full remission (De Winter et al. 2007). The second subcategory, depression with above-normal plasma AVP, was defined by the optimal cut-off level of the plasma AVP concentration for familial depression, and the clinical picture of this subcategory was characterised by correlating anxiety and retardation scores (Goekoop et al. 2006).

In this study, we tested whether the patients with depression with above-normal plasma AVP concentration are characterized by a personality dimension of the TCI representing a specific style of social behaviour. The TCI comprises three character dimensions, self-directedness (SD), cooperativeness (CO) and self-transcendence (ST), as well as four temperament dimensions, harm-avoidance (HA), novelty seeking (NS), reward-dependence (RD) and persistence (PER) (Cloninger et al. 1993). The dimensions of CO and RD represent selfreported styles of social behaviour. The subscales of the CO dimension assess 'social acceptance' versus 'intolerance', 'empathy' versus 'social disinterest', 'helpfulness' versus 'unhelpfulness', 'compassion' versus 'revengefulness' and 'pure-heartedness' versus 'self-serving'. The subscales of the RD dimension assess 'sentimentality' versus 'insensitivity', 'attachment' versus 'detachment' and

'dependence' versus 'independence'. Examples of items of these scales are: 'I can usually accept other people as they are, even if they are very different from me' or 'I like to help find a solution to problems so that everyone comes out ahead' and 'I would like to have warm and close friends with me most of the time' or 'If I am feeling upset I usually feel better around friends than when left alone'. A substantial contribution of genetic factors has been found in both dimensions (Ando et al. 2002, Ando et al. 2004, Gillespie et al. 2003). Although the dimension of HA has been found to predict general social adaptation in dyadic interaction (Tse et al. 2005), this dimension was hypothesized not to contribute to the validation of the subcategory of depression with above-normal plasma AVP as it represents the general vulnerability trait for all depressive disorders (De Winter et al. 2007).

Similar to our previous study of the relation between a subcategory of depression and TCI scores (De Winter et al. 2007), we were primarily interested in the TCI scores after full remission of depression. This method maximally eliminates state-dependent report bias and therefore offers an optimal estimation of the presumed premorbid personality. In addition, we searched for evidence of state-dependent reversible changes on the CO and RD dimensions during the transition from the depressed state to the condition of full remission.

2 Methods and materials

2.1 Subjects

We reanalysed the data of a subsample of the 89 patients investigated in a previous analysis (De Winter et al. 2004). All patients were newly referred to an in- and out-patient's clinic of Rivierduinen GGZ Leiden. They were recruited if a psychiatrist had made an initial diagnosis of major depression according to the DSM-IV, and if this diagnosis was subsequently confirmed by the investigator (RFP de W) using a semi-standardised interview. This among others comprised the DSM-IV criteria for major depression (American Psychiatric Association 1994), subtypes of major depression, and the Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg et al. 1978, Goekoop et al. 1992). Patients were included if they in addition rated at least 21 on the Montgomery Åsberg Depression Rating scale (MADRS) (Montgomery and Åsberg 1979), and consented to the protocol. Patients with organic disorder and patients with bipolar, schizoaffective or schizophrenic or other primary psychotic disorder were excluded, as were patients with a somatic disorder that could influence plasma AVP concentration, such as inappropriate anti-diuretic hormone (ADH) secretion. Depressed patients with a panic disorder were not included because they participated in a different research project. The presence of a severe personality disorder that by the first psychiatrist was assumed to hamper the treatment of the mood disorder, was an additional exclusion criterion.

In all, 86 of the 89 patients had full TCI data, 81 full AVP data and 78 full TCI and AVP data. These 78 patients were investigated in the first cross-sectional analysis of the present study. The first 70 of them were recruited for a 2-year longitudinal study (De Winter et al. 2006), and 58 patients were eventually available for cross-sectional evaluation after two years of follow-up. Written informed consent was obtained from all patients. The Ethical Committee of Leiden University Medical Centre (LUMC) approved the study protocol. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Educational level was classified in six categories (level 1 = low education to level 6 = University or postgraduate).

Normal control subjects (n = 86) were selected from a normative sample (Duijsens et al. 2000), which was at random recruited from the national telephone book as described in the study of the relation between the highly anxious-retarded depressive subcategory and personality (De Winter et al. 2007). For reason of comparability, the number of control subjects was kept the same as in that study.

2.2 *Personality*

The Dutch translation (Duijsens et al. 2000) of Cloninger's Temperament and Character Inventory (Cloninger et al. 1993) was used to assess the temperament dimensions of novelty seeking (NS), harm-avoidance (HA), reward-dependence (RD) and persistence (PER), and the character dimensions of self-directedness (SD), cooperativeness (CO) and selftranscendence (ST). The lists were filled in within 2 weeks after recruitment and every 6 months until 2-years after recruitment. Patients were asked to respond to the items 'as if they were in their premorbid state', to maximally reduce statedependent changes of response tendency.

2.3 *Treatment*

The therapy comprised pharmacotherapy or cognitive behavioural therapy in mild cases and both in more severe depression. If necessary, relational therapy, daytime treatment or clinical treatment was added. If at entrance a patient was already taking an antidepressant, that treatment was continued and increased to maximal dose. If this drug had to be changed because of lack of effect, drug withdrawal was performed after the first assessment of the study. The steps after the initial antidepressant comprised: 1) venlafaxine, 2) amitriptylin, 3) amitriptylin and lithium, 4) lithium and tranylcypromine and 5) electroconvulsive therapy.

To account for potential drug effects on plasma AVP and the cut-off level in particular, antipsychotic, antidepressant and benzodiazepine drug dosages at t1 were used as covariates in the analyses. To this end, they were transformed into equivalent dosages (haloperidol, imipramine and chlordiazepoxide equivalents) according to standard dosage ranges (Moleman and Birkenhaeger 1998).

2.4 *Plasma AVP*

As described before (De Winter et al. 2003), within 7 days of the CPRS interview, blood samples were drawn on a single day under standardised conditions between 09.00 a.m. and 9.30 a.m. and between 3.30 p.m. and 4.00 p.m. All patients refrained from ingesting alcohol and from undertaking strenuous physical exercise (sports) for 12 h before the study. They sat down 15 min before venipuncture. Smoking was not allowed for 30 min before venipuncture; eating and drinking were allowed ad libitum.

Blood was collected in 10-mL vacutainer tubes and immediately stored at 4 °C. Within 30 min, plasma was separated in a cooled centrifuge and stored at −80 °C. The determination of plasma AVP was based on radioimmunoassay (RIA) following peptide extraction using C-8 Bond ElutR cartridges (Analytichem International, Harbor City, CA, USA RIA was performed using a rabbit antiserum (coded W1E) with the following cross-reactivities: vasotocin 100%; (Cyt6)AVP-(3–9) 50%; (pGlu4, Cyt6)AVP-(4–9) 25%; (Cyt6)AVP-(5–9) 13%; AVP-(1–8), AVP-(1–7) and oxytocin undetectable. The detection limit of the extracted assay was 0.5 pg/mL plasma, and the intra-and inter-assay coefficients of variation were 9.9% and 15.9%, respectively. Patient and control samples were coded and assayed in a single run. For each patient, mean daytime plasma AVP level (plasma AVP) was computed from the morning and afternoon values. Above-normal plasma AVP was defined as any value >5.56 pg/mL corresponding with the ROC analysis relating familial depression to above-normal plasma AVP (Goekoop et al. 2006).

2.5 *Follow-up and outcome*

All patients were assessed with the CPRS at the beginning of the treatment (t1), after 6 weeks (t2) and than after 3, 6, 12, 18 and 24 months (t3–t7) as described before (De Winter et al. 2006, De Winter et al. 2007). TCI data were available for t1,t4, t5, t6 and t7. Intensity of depression was described by means of the MADRS. Outcome was defined as DSM-IV depression in full remission, defined by a maximum of two DSM-IV symptoms during at least the last 2 weeks (Frank et al. 1991). Partial remission was defined by a minimum of three and a maximum of four symptoms of major depression during at least the last 2 weeks. DSM-IV criteria were defined by corresponding CPRS items. For this purpose, the scores on the individual items were dichotomised: scores ≥ 3 were taken as representing the presence of a DSM-IV symptom. Increased appetite and weight were rated separately.

2.6 *Data analysis*

The analyses were identical to those of our previous TCI study (De Winter et al. 2007). We used only gender and age as covariates in analyses comparing depressed patients with normal controls, and in addition, recurrent depression, MADRS score and educational level in investigations comparing subgroups of depressed patients. As in a previous analysis of this sample, antipsychotic dosage at t1 was, after elimination of other treatment variables, eventually used, in addition, in analyses comparing depressed subgroups.

Pearson's chi-square was used to analyse the relation between subcategories of depression. MANCOVA using TCI scores as dependent variables and above-normal plasma AVP as independent variable was used to compare subcategories of depressed patients with normal controls and to compare subgroups of depressed patients at t1 and t7. Separate comparisons were used to detect the direction of differences found. Doubly multivariate analysis was used to test TCI differences over 2 years between depression with above-normal AVP and depression with normal AVP. These analyses were all carried out by SPSS for Windows 12.0 (SPSS Inc, Chicago, USA).

3 Results

3.1 Demographic and clinical data

Table 1 shows demographic characteristics of the 78 depressed patients. No statistically significant differences were found between the patients with above-normal and those with normal plasma AVP concentration. These 78 patients at t1 did not differ in these respects from the 70 patients at t1 who consented to participate in the follow-up study. The characteristics of these 70 patients have been described elsewhere (De Winter et al. 2006). In all, 16 of the 78 patients had above-normal plasma AVP at t1. Of the 70 patients who entered the follow-up study, 15 patients had above-normal plasma AVP at t1. They were the same 15 patients with initially above-normal AVP who could be evaluated after 2 years.

Table 2 shows the percentage of the patients who had antipsychotic, antidepressant and anxiolytic treatments, as well as the dosages of these treatments at t1. No significant differences were found between the subgroups with normal and above-normal plasma AVP concentration. Mean MADRS score at t1 was 30 (range: 21–47). Mean MADRS of depression with above-normal AVP was 33 (range 23–41).

Table 1
Demographic data of acutely depressed patients and the subgroups with above-normal and normal plasma vasopressin (AVP).

	Major Depression	Above-normal AVP	Normal AVP
	n = 78	n = 16	n = 62
age	39 (sd =12)	41 (sd = 12)	39 (sd = 11)
female	52 (67%)	10 (63%)	42 (68%)
educational level	3.4 (sd = 1.5)	3.4 (sd = 1.6)	3.4 (sd = 1.5)
inpatients	32 (41%)	6 (38%)	26 (42%)
recurrent depression	45 (58%)	10 (63%)	35 (57%)
MADRS t1	30 (sd = 6)	33 (sd = 7)	30 (sd = 6)

(Age in years (y); theoretical range for level of education: 1-6; MADRS = depression severity rating scale; sd = standard deviation).

Table 2
Number and percentages of patients with psychotropic drug treatment, as well as mean haloperidol, imipramine and chlordiazepoxide equivalent dosages and standard deviations (sd) in acutely depressed patients and subgroups with above-normal and normal plasma vasopressin (AVP).

	Major Depression	Above-normal AVP	Normal AVP
Antipsychotic treatment	11 (14%)	3 (19%)	8 (13%)
Haloperidol equivalents	0.5 (sd = 1.5)	1.2 (sd = 2.9)	0.3 (sd = 0.8)
Antidepressant treatment	45 (58%)	9 (56%)	36 (58%)
Imipramine equivalents	90.5 (sd = 101.7)	81.3 (sd = 101.8)	93.0 (sd = 102.3)
Anxiolytic treatment	41 (53%)	8 (50%)	33 (53%)
Chlordiazepoxide equivalents	20.8 (sd = 32.8)	13.6 (sd = 18.7)	22.6 (sd = 35.4)

3.2 Treatment data

At t1, 9 of the 16 patients with above-normal plasma AVP had an antidepressant drug and 36 of the 62 patients with normal plasma AVP. At t1, four patients with above-normal AVP had selective serotonin reuptake inhibitor (SSRI) treatment, three venlafaxine and two a tricyclic antidepressant (TCA). At t3, no patient had SSRI treatment (chi-square 4.521; P = 0.033) compared with 12 of the 49 patients with normal AVP), 7 had venlafaxine and 1 had a TCA. This shift towards venlafaxine may have been related with insufficient change of the high MADRS score at t1 of the patients on SSRI treatment (mean MADRS = 41 range: 40–41). The data suggest insufficient SSRI response in depression with above-normal plasma AVP.

3.3 TCI scores in depression with above-normal plasma AVP at t1

MANCOVA at t1, during the acute episode, showed that all depressed patients (n = 78) differed from matched controls on HA (F = 92.755; P < 0.001) and SD (F = 76.625; P < 0.001) and less strongly on RD (F = 5.885; P = 0.016) and CO (F = 5.118; P = 0.025). Covariates used were gender and age. Patients with above-normal AVP (n = 16) differed significantly from matched control subjects on HA (F = 23.956; P < 0.001), SD (F = 21.166; <0.001), RD (F = 8.466; P = 0.004) and CO (F = 8.052; P = 0.006) and rather weakly on NS (F = 4.354; P = 0.040).

The acutely depressed patients with above-normal plasma AVP (n = 16) differed also from all other depressed patients (n = 62) on RD (F = 5.183; P = 0.031) but not significantly on CO (F = 2.615; P = 0.110) if relations with age, gender, level of education, recurrent depression and MADRS score were accounted for. Separate logistic regression analyses showed that antidepressant and benzodiazepine dosages were not related with above-normal plasma AVP. However, antipsychotic dosage was non-significantly related (Wald = 3.226; P = 0.072) with above-normal AVP. If this variable was added to the MANCOVA as covariate, then the strength of the relation with RD increased slightly (F = 6.330; P = 0.014), whereas the relation with CO became slightly weaker (F = 2.050; P = 0.157). Separate comparison showed both RD and CO to be lower in depression with above-normal AVP than in the group of all other depressed patients (RD = 12.81 (SD = 4.32) versus RD = 15.13 (SD = 3.70) and CO = 29.19 (SD = 5.59) versus CO = 32.00 (SD = 6.13)). Separate analyses of the correlation between RD and CO at t1 and plasma AVP concentration at t1 showed that there was no such correlation in the whole group of depressed patients or in depression with above-normal plasma AVP.

3.4 TCI scores in fully remitted patients with initially above-normal plasma AVP after 2 years (t7)

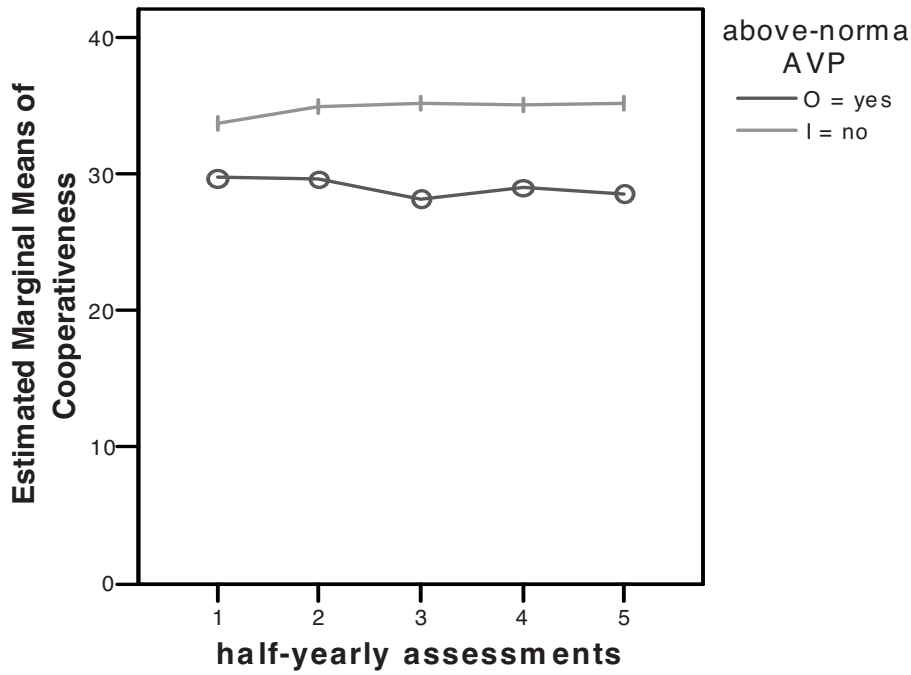
MANCOVA showed that fully remitted patients at t7 (n = 41) had only significantly higher HA compared with control subjects (MANCOVA: F = 19.94, df = 1 and P < 0.001; De Winter et al. 2007). MANCOVA also showed that after 2 years, fully remitted patients with initially above-normal plasma AVP (n = 11) had different CO (F = 9.357; P = 0.003) and HA (F = 4.387; P = 0.039) compared with control subjects, corrected for a significant effect of gender on HA (F = 18.286; P < 0.001) and RD (F = 4.129; P = 0.045) and a significant effect of age on CO (F = 9.357; P = 0.003) and HA (F = 4.387; P = 0.039). Separate comparison showed a lower CO (CO = 28.45; SD = 3.36 versus CO = 33.30; SD = 5.18) and a higher HA (HA = 20.45; SD = 8.52 versus HA = 15.38; SD = 7.13) in depression with above-normal AVP.

Compared with fully remitted patients with normal AVP at t7 (n = 30), fully remitted patients with initially above-normal plasma AVP (n = 11) differed on CO (F = 9.116; P = 0.005) and HA (F = 4.559; P = 0.040) (the effects of age, gender, level of education, recurrent depression and MADRS at t7 score being accounted for). MADRS score at t7 and recurrent depression were not related with CO at t7. Separate comparison showed that CO and HA were lower in remitted depression with above-normal AVP than in the

group of all other remitted patients (CO = 28.45 (SD = 3.36) versus CO = 34.53(SD = 54.89), and HA = 20.45 (SD = 8.52) versus HA = 22.13 (SD = 7.46)). If antipsychotic dosage at t1 was added to the MANCOVA as covariate, to account for its effect on above normal plasma AVP, then the strength of the relation with CO increased slightly (F = 9.462; P = 0.005), whereas the relation with HA became slightly weaker (F = 3.551; P = 0.070). If all patients with initially above-normal AVP concentration at t7 (n = 15) were compared with all other patients (n = 43), then they still differed uniquely on CO (F = 10.212; P = 0.003), despite the inclusion of the four not-fully-remitted patients (age, gender, level of education, recurrent depression and MADRS at t7 score, as well as the effect of antipsychotic at t1 accounted for).

Figure 1 illustrates the highly significant difference (F = 27.501; P < 0.001) between the CO scores of all patients with above-normal plasma AVP and all other patients during 2 years in the 53 patients with complete data (doubly multivariate analysis; repeated measures design with all TCI scores at five time points as dependent variables, above-normal plasma AVP as fixed factor and age, gender, level of education, recurrent depression, MADRS at t1 and antipsychotic dosage at t1 as covariates).

Figure 1
Cooperativeness in patients with above-normal plasma vasopressin (AVP) and all other patients assessed at 5 time points during 2 years of follow-up in 53 patients with complete data set.



4 Discussion

After full remission of depression, the subgroup of patients with initially above-normal plasma AVP concentration was characterised by low CO compared with both normal controls and the group of fully remitted patients with initially normal plasma AVP. This finding was strengthened by the highly significant difference between the repeated CO scores in the subcategory of depression with above-normal plasma AVP and the group of all other patients during the 2-year follow-up period. The low CO score after full remission did not relate to recurrent depression or depression severity and may therefore maximally correspond with the patient's premorbid personality. The combination of low CO and normal SD in this subcategory implies that their personality may be called autocratic or authoritarian (Cloninger et al. 1997; Cloninger et al. 1998). For the full picture of this presumably premorbid personality, one should further recognise that these patients also had the general personality characteristics of all patients with major depression: decreased SD and increased HA during the acute episode and high HA after full remission (De Winter et al. 2007). Regretfully, there are no plasma samples available to relate plasma AVP at t7 with HA and CO during full remission.

During the acutely depressed episode, the patients with above-normal plasma AVP concentration had low RD and low CO scores compared with normal controls and low RD compared with all other patients. The much lower statistical significance of the low CO score during the acute episode compared with the remitted state may be due to state-dependent response bias on the CO dimension in other patient group.

The contrast between low CO being detected both during the acute episode and after full remission and low RD being detected uniquely during the acute episode suggests a selectively state-dependent change in response tendency on the dimension of RD. The absence of a correlation between RD and plasma AVP concentration at t1 may be due to the incentive to score the TCI items as if in the premorbid condition but may also imply that other factor is involved. This factor could be reduced oxytocin release, as is suggested by the positive correlation between RD and plasma oxytocin in depression (Bell et al. 2006). The potential relation in this subcategory between increased concentration of plasma AVP and decreased concentration of plasma oxytocin, the two principal neurohypophyseal hormones that are centrally involved in social behaviour, is a question that deserves further investigation. Regretfully, there are no more plasma samples available to test the role of oxytocin.

The relations found between the biological marker of above-normal plasma AVP concentration on the one hand and familial depression (Goekoop et al. 2006), high HA and low CO and an anxious-retarded phenotype without intensitythreshold (Goekoop et al. 2006) on the other hand support a diagnostic concept that suggests a pathogenetic pathway centrally involving genetically increased AVP release. This warrants prospective investigations in subjects at increased familial risk, in which hypotheses are tested of the relation between the basal vasopressinergic regulation and both the premorbid social behaviour style and the response to stress. The differentiation between 'Pure Familial Depressive Disease' and 'Depression Spectrum Disorder' (Winokur 1997) may be useful in this context of familial depression, but also the potential association with bipolar disorder, which has been found related with an increased post-dexamethasone AVP concentration (Watson et al. 2006). The hypothesis that genetic factors determining AVP synthesis and release are involved in the low CO of depression with above-normal AVP is testable in principle because genetic factors have unexpectedly been found to explain the familial source of variation not only of the temperaments but also of the character

dimensions (Ando et al. 2002, Ando et al. 2004, Gillespie et al. 2003). Because of the high inter-assay variability of the basal AVP concentration, individual assignment may be improved by using postdexamethasone concentrations (Watson et al. 2006).

The emerging concept of a familial depressive disorder, involving genetically enhanced AVP release, low socialization and further inhibition of social behaviour during stressinduced increase of AVP release, suggests an analogy with the AVP-related behaviour of montane voles (Young 2002). Although it is not known whether these animals have by themselves already increased AVP release, they have a genetic polymorphism of the vasopressin-1a (V1a) receptor, basically restricted social behaviour, a severely reduced expression of the V1a receptor in brain structures involved in social reward related behaviour and increased self-grooming after administration of AVP (Young 2002) instead of the increase of social behaviour that is induced by AVP in the highly socialised prairie voles. A second animal model with potential relevance for genetic factors in depression with above-normal AVP may be that of the genetically increased release of AVP in the highly anxious inbred rat (Murgatroyd et al. 2004). The behavioural phenotype of this animal model has been found related with altered regulation of the promoter region of the AVP gene resulting in over-expression of AVP in the parvo- and magnocellular subdivisions of the hypothalamic paraventricular nucleus, which controls the activity of the HPA-axis. This animal model shows a remarkable analogy with that of depression with above normal plasma AVP as the former critically involves the combination of anxiety and passive avoidance and the latter mixed anxiety and retardation (Goekoop et al. 2006). Finally, depression with above-normal plasma AVP concentration may have an analogous genetic origin to that of autism, with its microsatellites of the V1a receptor gene (Yirmiya et al. 2006) and increased plasma AVP concentration (Momeni et al. 2007). The present findings support the validity of the depressive subcategory with above-normal plasma AVP, and the primary role in it of a genetically deficient vasopressinergic regulation of both the stress response and premorbid social behaviour. If these results are replicated, including the presumably insufficient SSRI response, this biological marker may be useful for the development of specific pharmacological treatment.

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