Eur Arch Psychiatry Clin Neurosci (2003) 253 : 185 – 192 DOI 10.1007/s00406-003-0423-8

ORIGINAL PAPER

Helena Prochazka · Hans Ågren

Self-rated aggression and cerebral monoaminergic turnover

Sex differences in patients with persistent depressive disorder

Received: 30 September 2002 / Accepted: 25 April 2003

Abstract *Objective* Outward-directed violence and impulsivity in humans and primates has frequently been related to abnormal brain monoaminergic turnover. Self-rated aggression is likely to be clinically relevant, and its psychobiological basis needs investigation. *Subjects* Sixty-six patients (40 women and 26 men) with persistent depressive disorder (PDD) were compared with 497 control subjects from the general Swedish population. *Methods* We administered the Aggression Questionnaire – Revised Swedish Version (AQ-RSV) to patients and control subjects. In patients, CSF 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy-5-hydroxyphenylglycol (MHPG) in CSF were analyzed. Total Aggression score and Aggression subfactors 'Physical Aggression', 'Verbal Aggression', 'Anger', and 'Hostility' were correlated with CSF concentrations of 5-hydroxyindoleacetic acid (5-HIAA), and 3-methoxy-5-hydroxyphenylglycol (MHPG). *Results* Overall, Hostility was positively related to CSF MHPG ($t = 2.27$, $p = 0.015$). Split by sex, Hostility was related with 5-HIAA in males ($r = 0.62$, $p = 0.003$), and with MHPG in females ($r = 0.38$, $p = 0.03$). Comparing self-rated aggression with age- and sex-matched data from the general Swedish population, the most prominent deviation was increased Hostility score among PDD patients. Among patients, all aggression factors were nominally higher in women than in men, with the most pronounced sex difference in Hostility ($t = -1.89$, $p = 0.04$). *Conclusions* Results suggest a clinically meaningful sex difference in a positive relationship between hostility and serotonergic/noradrenergic turnover in PDD patients.

Key words aggression · hostility · persistent depressive disorder · monoaminergic turnover · sex

H. Prochazka, MD
Göteborg University
Institute of Clinical Neuroscience, Department of Psychiatry
Sahlgrenska University Hospital/Mölndal
43180 Mölndal, Sweden

H. Ågren, MD, PhD
Karolinska Institutet
Neurotec Department, Division of Psychiatry
Huddinge University Hospital
14186 Stockholm, Sweden

Dr. Helena Prochazka (✉)
Styrfarten 14
41764 Göteborg, Sweden
Tel.: +46-737-054-899
E-Mail: prochazkahelena@hotmail.com

Introduction

The role of aggression in depressive disorders has been studied since the beginning of the last century, first in terms of inner-directed hostility in a psychodynamic context (Freud 1953) and then from a biological perspective (Coccaro et al. 1989). The most consistent reports of biochemical variables in depressed and suicidal patients concern decreased levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) (Åsberg et al. 1976; Träskman et al. 1981). The findings have been replicated in violent offenders, and healthy individuals with aggression (Linnoila et al. 1983; Virkkunen et al. 1990; Golden et al. 1991). A presumed link between reduced serotonergic function and aggression has been suggested to covary with features of suicidal behavior (Coccaro et al. 1989), but a recent study has shown reduced CSF concentrations of 5-HIAA also in aggressive patients with DSM-IV Axis I psychiatric disorders (APA 1994a) but no history of suicidal behavior (Stanley et al. 2000).

Extensive studies of the influence of genetic and environmental factors on the relationship between low CNS serotonergic activity and aggression in nonhuman primates have shown that a low CSF 5-HIAA concentration as quantified early in life is a powerful biological predictor of future excessive aggression, risk taking, and premature death (Higley et al. 1996, 1997). Studies of aggression in animal models indicate that not only the indoleamine serotonin and its metabolite but also catecholamines are involved in several types of aggressive

behavior, including self-directed aggression (Eichelman 1989). In humans, however, the possible significance of any monoamine for aggression and self-directed violent behavior is less evident, since social, cultural, and psychological factors are intricately involved in the physiology and neurochemistry of human behavior (Åsberg, 1994). Their close interplay tends to complicate attempts to measure, analyze, and assess human aggression.

The growing research interest in neurobiological mechanisms behind human aggression has created a demand for reliable and relevant measures of aggressive behavior. A number of psychiatric rating instruments have been developed to define and distinguish between types of aggression. Commonly used in psychiatric practice and research are observer scales, which are often criticized for overlooking all but the most blatant acts of aggression (Yudofsky et al. 1986), and self-report scales or questionnaires.

Originally, self-rating instruments have been developed to assess "level of aggressiveness", and have been found to be more suitable for measurement of hostile attitudes, anger and aggressive impulses than observer scales. Thus, psychometric instruments as Hostility Scale (Cook et al. 1954), Buss-Durkee Hostility Inventory (BDHI) (Buss et al. 1957) and Hostility and Direction of Hostility Questionnaire (HDHQ) (Caine et al. 1967), differing between outward and inward aggression, have been found advantageous for aggression studying in both healthy individuals and patients suffering from psychiatric or somatic disorders. By means of careful item selection, the self-report technique may allow for a balanced representation of spectacular and subtle aggressive behaviors, but the subjectivity and social desirability bias inherent in the method are obvious shortcomings (Bech et al. 1995). Since the 1960's, the most commonly used aggression questionnaire has been the Buss-Durkee Hostility Inventory (BDHI) (Buss et al. 1957) from which the Aggression Questionnaire (AQ) was developed after exploratory factor analysis (Buss et al. 1992). This instrument for assessment of self-rated aggression has been evaluated in Canada (Harris 1995), the Netherlands (Meesters et al. 1996), and Sweden (Prochazka et al. 2001).

The role of sex in aggression has been studied in the contexts of psychological, evolutionary, forensic and biological perspectives. Maccoby and Jacklin (1980) presented a meta-analysis of 32 observational studies of peer-directed aggression in children aged 6 and younger. Twenty-four studies reflected significant higher male aggression, and eight showed no differences in aggression between boys and girls. No study showed higher female aggression. Another view on sex aggression characteristics is presented in the forensic psychiatric context. Based on analysis of court records of 158 homicides over a 6-year-period, Jurik and Winn (1990) found considerable support for the "gender role" model. Compared to men, women are more prone to kill an intimate partner, most often in situations where the victim initiated the physical aggression.

The biological differences in aggression between sexes have been studied mostly in terms of sex steroid levels, with testosterone as most important hormone in androgen-induced aggression. Another neurochemical factor of relevance to sex and aggression is the monoaminergic system, but little is known about sex differences in the relationships between monoaminergic turnover and aggressive phenomena.

The present study was designed

- To investigate relationships between self-rated aggression and its subfactors on the one hand and, on the other, monoaminergic turnover as reflected by the CSF concentrations of the monoamine metabolites 5-HIAA, and 3-methoxy-4-hydroxy-phenylglycol (MHPG) in patients with persistent depressive disorder (PDD) (for lack of clear pre-hoc hypotheses, we did not focus on the dopamine metabolite homovanillic acid (HVA) in this study);
- To compare the self-rated aggression measured by the AQ-RSV in patients with PDD with self-rated aggression in the general Swedish population; and
- To analyze these relationships in a sex perspective.

Methods

Patients

Included in this study were 66 patients (40 women and 26 men, aged 19–82, mean ± SD: 44.5±12.9), referred by psychiatrists to a diagnostic research unit for affective disorders at Sahlgrenska University Hospital in Mölndal, Sweden, between September 1996 and December 1999 for a 5-day inpatient investigation period. All patients met the DSM-IV criteria for major depression, which in all cases had persisted for 2 years or longer. All had tried at least two antidepressant drug regimes at adequate doses and therapy periods. None had an Axis II diagnosis. All patients had discontinued antidepressant medication for a minimum of 2 weeks before admission: 16 patients for more than 4 weeks and 50 patients for 2–4 weeks before the study.

Medical history, diagnostic data on personality traits and psychiatric disorders were obtained from medical files and personal interviews. Patients were assessed by means of the Karolinska Scales of Personality (KSP) (Schalling et al. 1993) and the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott et al. 1978). SADS items were converted into scores for the Hamilton Depression Rating Scale (HDRS) according to Endicott and coworkers (Endicott et al. 1981).

No significant sex difference was found in age, body mass index (BMI), or severity of symptoms during the most difficult week of a current or recent depressive episode (HRDS "worst week" [WW]) or during the week before investigation (HRDS "past week" [PW]), or in confirmed history of suicide attempts. The mean HDRS scores were 23.7±5 for the HRDS WW and 18.4±5.9 for the HRDS PW in the entire study population. Thirty-nine percent (26 of 66 patients) displayed melancholic features (Table 1).

Assessment of self-rated aggression

Self-rated experiences of aggression were assessed by means of the AQ instrument (Buss et al. 1992) translated, adapted, and evaluated in the general Swedish population. As described in a previous study (Prochazka et al. 2001), the revised Swedish version of the AQ (AQ-RSV) was mailed to 800 individuals, 20–40 years old, randomly selected from the Swedish population register. The questionnaire was completed by 497 persons (64 % of 781 ascertained recipients), 268

Table 1 Characteristics in men and women with persistent depressive disorder (PDD)

Variables	All patients (n = 66) (mean ± SD)	Females (n = 40) (mean ± SD)	Males (n = 26) (mean ± SD)	Sex difference p value (t test)
Age (years)	44.5 ± 12.9	44.8 ± 12.6	44.1 ± 13.5	NS
Weight (kg)	74.1 ± 15.6	68.2 ± 13.1	83.1 ± 15.1	$p < 0.001$
Height (m)	1.73 ± 9.8	1.67 ± 0.05	1.82 ± 0.08	$p < 0.001$
BMI (kg/m^2)	24.5 ± 4.0	24.1 ± 3.7	25.0 ± 4.4	NS
HDRS "worst week"	23.7 ± 5.0	24.4 ± 4.9	22.5 ± 5.2	NS
HDRS "past week"	18.4 ± 5.9	18.7 ± 6.2	18.0 ± 5.6	NS

women and 229 men. The 29 items of the questionnaire are randomly arranged and measure four aggression factors: Hostility (8 items), Anger (7 items), Verbal Aggression (5 items), and Physical Aggression (9 items). The originally 5-point Likert item-standard of the American AQ was reduced to 4 scale steps (1 = "least characteristic", 2 = "some characteristic", 3 = "more characteristic", 4 = "most characteristic"), which had negligible effect on the correlation analyses between the Swedish and American data. The 4-point scale is also advantageous in that neutral answers are avoided. The internal consistency of the four aggression subscales and the total score was evaluated by Cronbach's alpha coefficients. All the alpha coefficients for the AQ-RSV indicated considerable internal consistency, and were comparable with AQ (Prochazka et al. 2001).

The scale results in the present study were evaluated in two ways: as raw scores, and compared to the corresponding values in randomly selected individuals from the general Swedish population, the possible influence of the different ages between patients and the population being covaried out (aggression decreases with age). Each patient's aggression score was compared with normative aggression score, i. e. age- and sex-specific regression value, statistically determined to 1 (Prochazka et al. 2001). Table 2 shows the scores in the Swedish population as well as in the patients.

Standardized CSF collection

No patient displayed signs of increased intracranial pressure as checked by ophthalmoscopy. Lumbar punctures were made at about 9 a. m. in the L3/L4 or L4/L5 interspace of the vertebral column with the patient lying on her/his side in bed after resting and fasting since midnight. A 12 ml sample of CSF was drawn with a 0.7 or 0.9 mm needle, gently mixed, immediately put on ice, and delivered to the neurochemistry laboratory within one hour.

Analysis of monoamine metabolites

The monoamine metabolites 5-HIAA and MHPG were routinely analyzed by means of high-performance liquid chromatography (HPLC) with electrochemical detection (Blennow et al. 1993). All monoamine metabolite concentrations were within normal reference limits.

Statistical analyses

Descriptive statistics was assessed with SPSS Release 10.1 for MS Windows (Norusis 1990). The predictive power of sex and monoamine metabolites on self-rated aggression was tested by means of analyses of covariance (ANCOVAs) using the SAS StatView package. Furthermore, we calculated the partial correlations between CSF monoamine metabolites and aggression measures, controlling for effects of sex, age, BMI, categorized time variable of length of drug-free period before investigation, melancholic features, and history of suicide attempts. The same analyses were also made separately in men and women. The third part of the statistical analysis of self-rated aggression was a comparison between the Swedish normal population and the PDD study population by sex, using t tests for independent samples.

Results

Self-rated aggression and monoaminergic turnover in male and female PDD patients

To analyze relationships between biological and aggression variables, the age- and sex-matched normative aggression data were used. Table 3 shows the results from comparing aggression subfactors measured by AQ-RSV with CSF variables 5-HIAA and MHPG. Study of the partial regression coefficients of 5-HIAA and MHPG when predicting a subfactor (and influence of sex thus partialed out) demonstrates a significant positive relationship between MHPG and Hostility, and a weaker one at trend probability with 5-HIAA. The effects remained after also partialling out age, BMI, categorized time variable of length of drug-free period before study start, melancholic features, and history of suicide attempts.

Fig. 1 illustrates the regressions between the studied CSF metabolites and the Hostility subfactor. A distinct

Table 2 AQ-RSV aggression scores in the general Swedish population and PDD patients. Raw scores, not corrected for age

	General Swedish Population (Means±SD)			PDD Patients (Means±SD)		
	All N = 497	Male N = 229	Female N = 268	All N = 66	Male N = 20	Female N = 46
Total Aggression	53.5 ± 11.6	55.2 ± 12.3	51.9 ± 10.7	59.1 ± 11.7	59.9 ± 11.0	58.6 ± 12.3
Physical Aggression	14.8 ± 4.9	16.5 ± 5.3	13.4 ± 4.0	14.6 ± 4.4	15.2 ± 4.1	14.1 ± 4.6
Verbal Aggression	11.1 ± 2.4	11.3 ± 2.5	11.0 ± 2.3	10.5 ± 2.7	10.9 ± 2.2	10.2 ± 3.0
Anger	13.5 ± 3.8	13.1 ± 3.8	13.8 ± 3.8	15.2 ± 3.8	15.0 ± 3.5	15.3 ± 4.0
Hostility	14.0 ± 4.2	14.3 ± 4.3	13.8 ± 4.2	18.8 ± 5.4	18.9 ± 5.4	18.8 ± 5.5

Table 3 Monoamine metabolites predicting aggression measures by partial regressions, influence of sex being partialled out (● denotes $p > 0.10$). Only main effects shown since no interactions between sex and metabolites were significant

	Physical aggression*		Verbal aggression*		Anger*		Hostility*	
	t	p	t	p	t	p	t	p
CSF HIAA	−0.48	●	0.70	●	−0.99	●	1.74	0.088
CSF MHPG	−0.40	●	−0.33	●	0.09	●	2.27	0.015

* Age- and sex-matched aggression scores, compared with normative value 1 in the general Swedish population

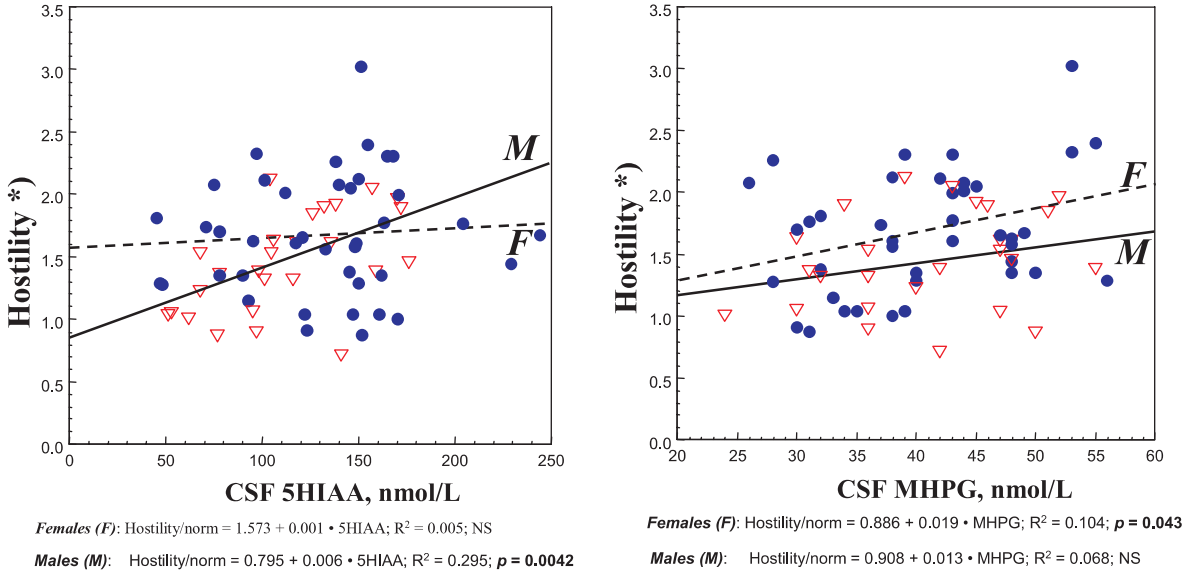

Fig. 1 Linear regressions between CSF metabolites 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy-4-hydroxy-phenylglycol (MHPG), and the Hostility subfactor in patients with persistent depressive disorders (PDD)
*) Age- and sex-matched aggression score, compared with normative value of 1 in the general Swedish population
Females (F) filled circles; *Males (M)* open triangles

sex difference was found: CSF 5-HIAA was positively and significantly correlated with Hostility in the men (CSF 5-HIAA: $r = 0.54$, $p = 0.0042$), but the correlation was not significant in the women. The opposite sex situation was seen in the relationship between the CSF MHPG and Hostility ($r = 0.32$, $p = 0.043$ in women versus $r = 0.26$, NS in men), but the difference between the regression slopes of CSF 5-HIAA versus Hostility split for sex did not quite reach significance and the other slopes showed no difference ($p > 0.10$).

Self-rated aggression in the general Swedish population and in PDD patients

As compared to normative data from Swedish population, the PDD patient group showed noteworthy higher values in all aggression factors, except for Verbal Aggression and Anger, with the most prominent difference in Hostility (entire PDD patient group 1.58, male patient group 1.43, female patient group 1.67).

As concerns sex differences within study groups, the self-rated aggression in general Swedish population measured with AQ-RSV showed sex differences in all Aggression factors. Men scored higher than women on Total Aggression, Physical Aggression, Hostility, and Verbal Aggression, while the reverse was found for Anger (Table 4a).

The aggression scores within the PDD patient group showed unexpected sex differences in that women with PDD had higher scores on all Aggression factors: slightly higher scores on Total Aggression and Anger, higher on Verbal Aggression and Physical Aggression, with the most prominent, significant, difference in Hostility score (Table 4a).

When compared self-rated aggression in sex perspective in the whole study sample, the significantly higher scores have been found in the PDD patient group, both in male and female, concerning Total Aggression, Anger, and Hostility factors (Table 4b).

Discussion

Several previous studies have supported the hypothesis that covert aggression/hostility is an integral factor in the development of depression (Perris et al. 1983; Wolfersdorf et al. 1998), but little is known about sex differences in the interrelationships between depressive and aggressive symptoms, and even less has been re-

Table 4 Self-rated aggression analyzed by sex in patients with persistent depressive disorder (PDD) and control subjects (CS) from general Swedish population. t tests for independent samples

a Sex comparisons in CS sample and in PDD patient group (males vs females)

Aggression factors	CS sample (n = 497) (229 males, 268 females) t-test, p-value (df = 495)	PDD patients (n = 66) (26 males, 40 females) t-test, p-value (df = 64)
Total Aggression	t = 3.20, p = 0.08 (m > f)	t = –0.45, NS (f > m)
Physical Aggression	t = 7.44, p < 0.001 (m > f)	t = –1.03, NS (f > m)
Verbal Aggression	t = 1.85, p = 0.07 (m > f)	t = –0.90, NS (f > m)
Anger	t = –2.08, p = 0.018 (f > m)	t = –0.38, NS (f > m)
Hostility	t = 1.26, NS (m > f)	t = –1.89, p = 0.04 (f > m)

b Sex comparisons between control subjects (CS) from general Swedish population and patients with persistent depressive disorder (PDD). CS males vs PDD males, CS females vs PDD females

Aggression factors	Male study group (n = 255) (229 CS males, 26 PDD males) t test, p value (df = 253)	Female study group (n = 308) (268 CS females, 40 PDD females) t test, p value (df = 306)
Total Aggression	t = –1.84, p < 0.001 (PDD males > CS males)	t = –3.57, p < 0.001 (PDD females > CS females)
Physical Aggression	t = 1.21, NS (CS males > PDD males)	t = –1.01, NS (PDD females > CS females)
Verbal Aggression	t = 0.98, NS (CS males > PDD males)	t = 1.81, NS (CS females > PDD females)
Anger	t = –2.39, p = 0.018 (PDD males > CS males)	t = –2.33, p = 0.03 (PDD females > CS females)
Hostility	t = –5.01, p < 0.001 (PDD males > CS males)	t = –6.71, p < 0.001 (PDD females > CS females)

ported about sex differences in the presumed relationships between monoaminergic turnover and aggressive phenomena in psychiatric patients.

Our present findings confirm previously reported sex differences in self-rated aggression (Prochazka et al. 2001; Rossi et al. 1986). Furthermore, they indicate that the pathological process in a psychiatric disorder such as PDD may induce specific forms of aggression, such as hostility. Lastly, distinct sex differences are indicated in the linkage between aggressive symptoms and central monoaminergic turnover.

Previous studies on monoaminergic turnover and self-rated aggression in both sexes

Findings in general populations

Møller and co-workers (1996) compared 27 women and 25 men regarding CSF monoamine metabolites and aggression rated by the 41-item Kinsey Institute Reaction List II Aggression, KIRL (Reinisch et al. 1993). Two significantly positive correlations were found among 10 significant partial correlation coefficients corrected for age, height, and weight: one between CSF 5-HIAA and "extroverted aggression" (outward-directed aggression comparable with Physical Aggression in AQ-RSV) in women and the other between CSF MHPG and "moral aggression" in men. The samples were too small for conclusions concerning sex differences, but the results may indicate more obvious links between elevated levels of CSF 5-HIAA and extroverted aggression in healthy women than in healthy men.

Other studies have noted lower metabolite concentrations in men than in women (Roy et al. 1988a; Ågren et al. 1986). Contradicting our findings is the report of a negative correlation between introverted aggression and CSF 5-HIAA in both sexes (Roy et al. 1988b). The authors suggested that introverted aggression might be regarded as "pathological" aggression, i. e. related to psychiatric disorders. Since CSF HVA is highly significantly and positively correlated with CSF 5-HIAA, it is not evident whether a correlation with HVA or 5-HIAA is specific to either metabolite. In fact, earlier studies have suggested that the dependence of CSF HVA on 5-HIAA indicates a serotonergic control of dopamine turnover, i.e. "CSF 5-HIAA drives CSF HVA" (Ågren et al. 1986). Since specific information from CSF HVA is so hard to evaluate, by much previous research, we have omitted it from our analysis.

Findings in psychiatric patients

Aggressive behavior may be encountered in a wide range of psychiatric illness. According to the multi-axial diagnostic system (DSM-IV) aggression is an indicator of severe maladaptive social functioning, which forms the symptomatology and affects the consequences of the illness (APA 1994b). In an unselected Swedish birth cohort, Hodgins (1992) demonstrated that the risk of being charged with a violent crime was four times higher in men, and 27 times higher in

women, with a major mental disorder than in mentally healthy individuals.

Special attention has been focused on the role of neurotransmitters and their CSF metabolites in aggression since the 1950's, when Woolley and Shaw (1954) suggested that an abnormal serotonin metabolism might trigger development of psychotic illness. CSF 5-HIAA, the most commonly studied marker, is thought to reflect cerebral serotonin turnover. The best-documented clinical association with any kind of monoaminergic turnover in psychiatric disorders is that between low CSF concentrations of 5-HIAA and aggressive suicide attempts (Åsberg et al. 1976; Träskman et al. 1981; Brown et al. 1982), but since only men participated in most of the published studies, sex differences cannot be analyzed in retrospect.

Hostility as a predictive factor for somatic and psychiatric illness

The aggression subfactor Hostility in AQ-RSV defines an attitude. Early in the history of psychiatry, hostility was interpreted as a manifestation of an inverted and self-destructive human force. During the last decade, hostility has also been studied within somatic medicine as sex differences were discovered in the symptomatology of heart disease and risk of myocardial infarction (MI). Myrtek (2001) presented meta-analyses of published prospective studies about association between Type A personality or hostility, and cardiovascular heart disease (CHD) until the end of 1998. He found that hostility is significantly associated with CHD.

Lahad and co-workers (1997) have examined 1277 postmenopausal women with a history of MI and found a significant linear association between Hostility and increased risk of MI. These results have been confirmed by a recent epidemiological prospective study performed by Chaput and co-workers (2002) evaluating the role of hostility as a risk factor for secondary CHD in postmenopausal women. When comparing women with low and high Cook-Medley hostility scores, women with the highest score were twice as likely to have had a myocardial infarction, and hostility was found to be an independent risk factor for recurrent CHD events in postmenopausal women.

Relationships between monoaminergic turnover and hostility have been studied by Roy and coworkers (1988). In a small sample (10 men and 7 women), they demonstrated an association between low CSF 5-HIAA and increased "urge to act out hostility" in normal volunteers, among whom the men had lower CSF concentrations of both 5-HIAA and HVA than women.

In the present study, the predominant outcome of all statistical analyses was the predictive power of sex for Hostility and for Anger, and of CSF 5-HIAA and CSF MHPG for Hostility, in PDD patients. Though the lack of previous data on this issue prevents firm conclusions, our results are suggestive of a clinically meaningful sex difference in the neurobiological substrate of hostility and anger.

Self-rated aggression, "stress-related" disorders and monoaminergic turnover

Except for Verbal aggression and Anger, the AQ-RSV scores were generally higher in PDD patients than in age- and sex-matched members of the general Swedish population. A striking sex difference was noted in the female dominance on the majority of aggression scales in the PDD group. These two observations correspond to AQ-RSV findings in a recent study on mass-displaced Kosovars diagnosed with post-traumatic stress disorder (PTSD) (Ekblad et al. 2001). The chronic nature of PDD and PTSD and the burden of long-term stress might be common denominators. In both disorders, patients tend to demonstrate "uncertainty" and lack ability to plan ahead. Presumably, the higher Hostility scores in female patients might reflect less reluctance to express emotions verbally among women than among men.

We have for the first time demonstrated a sex difference in the neurobiological substrate of underlying aggression in patients with PDD. In a previous study of PDD patients, a blunted prolaction response to fenfluramine challenge indicated an altered serotonergic mechanism (Prochazka et al. 2000). We interpret the altered monoaminergic function as a possible consequence of a non-remitting course of illness. Chronicity per se may be a factor of crucial importance for understanding the results from the present study. The acute and chronic stress responses with the hypothalamus-pituitary-adrenaline (HPA) axis activation and inhibition might be differently regulated in men and women. Finally, the positive relationships between an aggression subfactor and CSF metabolites may reflect phenomena unrelated to the earlier well-described links between impulsivity and low CSF metabolites.

Verification of the sex differences found in this study would require a new and larger patient sample and a reference group examined with the same rating instruments. Causal directions in the relationships cannot be investigated with the present methodology. Nevertheless, altered cerebral serotonergic and/or noradrenergic turnover appears to be an important factor behind elevated degrees of self-experienced aggression (especially Hostility) in PDD, maybe also in other "stress-related" psychiatric problems. To resolve these issues, prospective studies need to include further neurobiological aspects, such as hormones, HPA-axis, and female hormonal cycles, and to explore specific patterns of the PDD course.

Acknowledgments We thank Ewa Ericson, Magnus Sjögren MD, PhD, Olof Zachrisson MD, and Madeleine Zöller MD, PhD for help in assessing patients. Financial support was provided by the Swedish Medical Research Council (grant 6604 to Hans Ågren), the Swedish Psychiatric Association, and Salus/Ulf Nilsonnes Foundation for Medical Research.

References

1. American Psychiatric Association (1994a) Depressive disorders. In: Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). American Psychiatric Press, Washington, DC, 167–172
2. American Psychiatric Association (1994b) Total assessment of functioning scale. In: Quick Reference to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). American Psychiatric Association, Washington DC
3. Bech P, Mak M (1995) Measurements of impulsivity and aggression. In: Hollander E, Stein DJ (eds) Impulsivity and Aggression. John Wiley & Sons, New York, pp 25–41
4. Blennow K, Wallin A, Gottfries CG, Karlsson I, Månsson JE, Skoog I, Svennerholm L, Wikkelsö C (1993) Cerebrospinal fluid monoamine metabolites in 114 healthy individuals, 18–88 years of age. Eur J Neuropsychopharmacol 3:55–61
5. Brown GL, Ebert M, Goyer PF, Jimerson D, Klein W, Bunney W, Goodwin FK (1982) Aggression, suicide, and serotonin: relationship to CSF amine metabolites. Am J Psychiatry 139:741–746
6. Buss AH, Durkee A (1957) An inventory for assessing different kinds of hostility. J Consult Psychol 21:343–349
7. Buss AH, Perry M (1992) The Aggression Questionnaire. J Pers Soc Psychol 63:452–459
8. Caine TM, Foulds GA, Hope K (1967) Manual of the Hostility and Direction of Hostility Questionnaire. University of London Press, London
9. Chaput LA, Adams SH, Simon JA, Blumenthal RS, Vittinghoff E, Lin F, Loh E, Matthews KA (2002) Hostility predicts recurrent events among postmenopausal women with coronary heart disease. Am J Epidemiol 15156 (12):1092–1099
10. Coccaro EF, Siever LJ, Klar HM, Maurer G, Cochrane C, Cooper TB, Mohs RC, Davis KL (1989) Serotonergic studies in patients with affective and personality disorders. Arch Gen Psychiatry 46:587–599
11. Cook WW, Medley DM (1954) Proposed hostility and pharisaic-virtue scales for the MMPI. J Appl Psychol 38:414–418
12. Eichelman B (1989) Neurochemical and psychopharmacologic aspects of aggressive behaviour. In: Meltzer H (ed) Psychopharmacology: The third generation of progress, Raven Press, New York, pp 697–704
13. Ekblad S, Prochazka H (2001) Self-rated aggression and its relationship to PTSD among mass displaced adults from Kosovo in Sweden. Manuscript Karolinska Institutet, Department of Psychosocial Medicine, Stockholm
14. Endicott J, Cohen J, Fleiss J, Sarantakos S (1981) Hamilton Depression Rating Scale extracted from regular and changed versions of the Schedule for Affective Disorders and Schizophrenia. Arch Gen Psychiatry 38:98–103
15. Endicott J, Spitzer RL (1978) A diagnostic interview. The Schedule for Affective disorders and Schizophrenia. Arch Gen Psychiatry 35:837–844
16. Freud S (1953) Mourning and melancholia (1915). In: Complete Psychological Works, Hogarth Press, London, pp 152–172
17. Golden RN, Gilmore JH, Corrigan HM, Ekström RD, Knight BT, Garbutt JC (1991) Serotonin, suicide, and aggression: clinical studies. J Clin Psychiatry 52(Suppl):61–69
18. Harris JA (1995) Confirmatory factor analysis of the Aggression Questionnaire. Behav Res & Ther 33:991–993
19. Higley JD, Linnoila M (1997) Low central nervous serotonergic activity is traitlike and correlates with impulsive behaviour. A nonhuman primate model investigating genetic and environmental influences on neurotransmission. Ann N Y Acad Sci 836:39–56
20. Higley JD, Mehlman PT, Higley SB, Fernald B, Vickers J, Lindell SG, Taub DM, Suomi SJ, Linnoila M (1996) Excessive mortality in young free male nonhuman primates with low cerebrospinal fluid 5-hydroxyindoleacetic acid concentrations. Arch Gen Psychiatry 536:537–543
21. Hodgins S (1992) Mental disorder, intellectual deficiency, and crime. Arch Gen Psychiatry 49:476–483
22. Jurik NC, Winn R (1990) Gender and homicide: a comparison of men and women who kill. Violence Vict 54:227–242
23. Lahad A, Heckbert SR, Koepsell TD, Psaty BM, Patrick DL (1997) Hostility, aggression and the risk of nonfatal myocardial infarction in postmenopausal women. J Psychosom Res 43:183–195
24. Linnoila MI, Virkkunen M, Scheinin M, Nuutila A, Rimón R, Goodwin FK (1983) Low cerebrospinal fluid 5-hydroxyindolacetic acid concentrations differentiate impulsive from non-impulsive violent behaviour. Life Sci 33:2609–2614
25. Maccoby EE, Jacklin CN (1980) Sex differences in aggression: a rejoinder and reprise. Child Dev 514:964–980
26. Meesters C, Muris P, Bosma H, Schouten E, Beuving S (1996) Psychometric evaluation of the Dutch version of the Aggression Questionnaire. Beh Res & Ther 34:839–843
27. Myrtek M (2001) Meta-analyses of prospective studies on coronary heart disease, type A personality, and hostility. Intern J Cardiol 79(2–3):245–251
28. Møller SE, Mortensen EL, Breum L, Alling C, Larsen OG, Bøge-Rasmussen T, Jensen C, Bennicke K (1996) Aggression and personality: association with amino acids and monoamine metabolites. Psychol Med 26:323–331
29. Norusis M (1990) SPSS Base System User's Guide, SPSS Inc, Chicago
30. Perris C, Eisemann M, Ericsson U, Knorring Lv, Perris H (1983) Patterns of aggression in the personality structure of depressed patients. Arch Psychiatr Nervenkr 233:89–102
31. Prochazka H, Sjögren M, Ågren H (2000) Oral d-fenfluramine test in treatment refractory depression. Plasma prolactin response compared in patients with and without suicide attempts and in a healthy reference group. J Affect Disord 57:201–208
32. Prochazka H, Ågren H (2001) Aggression in the general Swedish population, measured with a new self-rating inventory: the Aggression Questionnaire – Revised Swedish Version (AQ-RSV). Nord J Psychiatry 55:17–23
33. Reinisch JM, Mortensen EL, Sanders SA (1993) Prenatal development project. Acta Psychiatr Scand 87(suppl 370):54–61
34. Rossi AM, Jacobs M, Monteleone M, Olsen R, Surber RW, Winkler EL (1986) Characteristics of psychiatric patients who engage in assaultive or other fear-inducing behaviours. J Nerv Ment Dis 174:154–160
35. Roy A, Adinoff B, Linnoila M (1988a) Acting out hostility in normal volunteers: negative correlation with levels of 5-HIAA in cerebrospinal fluid. Psychiat Res 24:187–194
36. Roy A, Adinoff B, Roehrich L, Lamparski D, Custer R, Lorenz V, Barbaccia M, Guidotti A, Costa E, Linnoila M (1988b) Pathological gambling: a psychobiological study. Arch Gen Psychiatry 45:369–373
37. Schalling D, Edman G (1993) The Karolinska Scales of Personality (KSP): an inventory for assessing temperament dimensions associated with vulnerability for psychosocial deviance, Karolinska Institutet, Department of Psychiatry, Stockholm
38. Stanley B, Molcho A, Stanley M, Winchel R, Gameroff MJ, Parsons B, Mann JJ (2000) Association of aggressive behavior with altered serotonergic function in patients who are not suicidal. Am J Psychiatry 157:609–614
39. Träskman L, Åsberg M, Bertilsson L, Sjöstrand L (1981) Monoamine metabolite in CSF and suicidal behaviour. Arch Gen Psychiatry 38:631–636
40. Virkkunen M, Linnoila M (1990) Serotonin in early onset, male alcoholics with violent behaviour. Ann Med 22:327–331
41. Wolfersdorf M, Kiefer A (1998) Depression and aggression. A control group study on the aggression hypothesis in depressive disorders based on the Buss-Durkee Questionnaire. Psychiatr Prax 25(5):240–245
42. Woolley D, Shaw E (1954) A biochemical and pharmacological suggestion about certain mental disorders. Proc Natl Acad Sci USA 40:228–231
43. Yudofsky S, Silver J, Jackson W, Endicott J, Williams D (1986) The overt aggression scale for the objective rating of verbal and physical aggression. Am J Psychiatry 143:35–39
44. Ågren H, Mefford IN, Rudorfer MV, Linnoila M, Potter WZ (1986) Interacting neurotransmitter systems. A non-experimental approach to the 5-HIAA-HVA correlation in human CSF. J Psychiat Res 20:175–193

45. Åsberg M (1994) Monoamine transmitters in human aggressiveness and violence: a selective review. Crim Behav Mental Health 4:303–327

46. Åsberg M, Träskman L, Thorén P (1976) 5-HIAA in the cerebrospinal fluid: a biochemical suicide predictor? Arch Gen Psychiatry 33:1193–1197