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Personality Factors Predisposing to Depression Correlate Significantly Negatively with M1-Muscarinic and β-Adrenergic Receptor Densities on Blood Cells

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Summary. A relationship between psychological and neurobiological predisposition factors for affective disorders has been suggested. The aim of the present study was to test this hypothesis. As predisposition measures of affective disorders, muscarinic and β-adrenergic receptors densities on blood cells and personality traits were determined in 16 male volunteers. The Minnesota Multiphasic Personality Inventory (MMPI), Freiburger Personality Inventory (FPI), and Premorbid Personality Inventory (PPI) were used for personality assessment. The erythrocyte muscarinic receptor density (mainly M1 subtype) correlated highly significantly negatively with depression on the MMPI ($r = -0.71$; $P < 0.001$) as well as significantly positively with reactive aggressiveness (dominance) on the FPI ($r = 0.48$; $P < 0.05$) and extraversion on the PPI ($r = 0.46$; $P < 0.05$). The β-adrenoceptor density on lymphocytes correlated significantly negatively with spontaneous aggressiveness ($r = -0.51$; $P < 0.05$) on the FPI. These results are the first evidence that premorbid personality traits of depressives are related to M1-muscarinic and β-adrenergic receptors densities. It is speculated that decreased β-adrenergic receptor densities might predispose an individual to major depression whereas a decrease of M1-muscarinic receptor densities could play a role in the development of minor depressions. The findings of the present study are compatible with the postulated relationship between personality and neurobiological predisposition factors of depressive disorders. They suggest the participation of neurobiological factors in the development of personality traits predisposing to depression. However, they seem to be nonspecific for depression and are probably neither a sufficient nor a necessary cause of this disorder. Additional biological or psychological factors seem to be required for the development of clinical depressions.

Key words: Muscarinic receptors – β-Adrenoceptors – Personality disorders – Aggressiveness – Affective disorders – Depression – Predisposition – Vulnerability

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Introduction

The role of genetic predisposition in the genesis of affective disorders is well-established (Zerbin-Rüdin 1980a; Nurnberger and Gershon 1984; Gershon et al. 1986). However, what is inherited is unknown. On the psychological level, personality factors, and on the neurobiological level, reduced monoamineoxidase activity, serotonic deficiency, and cholinergic supersensitivity have been postulated to play a role in the predisposition to affective disorders (Buchsbaum et al. 1976; van Praag 1980; Sitaram et al. 1982). The genetic nature of personality factors (Vandenberg 1967; Zerbin-Rüdin 1980) suggests a biological basis and consequently a possible relationship between personality and neurobiological predisposition factors. The demonstration of such a relationship might give us an indication of what is inherited and should

improve our understanding of the mechanisms involved in the pathogenesis of affective disorders.

With regard to personality factors of affective patients, oral and anal or obsessional character traits such as orderliness have been described clinically and are commonly found in endogenous depressive patients (Chodoff 1972; Blankenburg 1973; Mendelson 1974; Tellenbach 1980; von Zerssen 1982). Psychometrically, personality questionnaires revealed higher scores on introversion, orderliness, and premorbid aggressiveness in major depressives (Kendell and Discipio 1968; Paydel et al. 1976; Frey 1977; von Zerssen 1976, 1980; Angst and Clayton 1986; Hirschfeld 1986).

With regard to neurobiological factors, a growing body of evidence has accumulated in favor of noradrenergic and cholinergic disturbances in depressions (Beckmann 1978, 1986; Waldmeier 1981; Sitaram et al. 1984; Risch and Janowsky 1984). According to the catecholamine deficiency hypothesis (Schildkraut 1965; Bunney and Davis 1965; Matussek 1966), depression is produced by a deficiency or subsensitivity of the catecholaminergic, specifically of the noradrenergic, system. On the other hand, Sulser et al. (1978) suggested that depression might be caused by catecholaminergic hypersensitivity since antidepressants reduce the sensitivity of β-receptors in vitro.

The adrenergic-cholinergic imbalance hypothesis of affective disorders (Janowsky et al. 1972) postulates that an increased ratio of cholinergic to noradrenergic activity causes depression. The evidence in favor of this hypothesis is based on drug effects and physiological abnormalities in affective patients. In short, most potent antidepressants show anticholinergic effects (Snyder and Yamamura 1977), anticholinergics have been shown to exert antidepressive effects (Gisselmann et al. 1975; Kasper et al. 1981; Beckmann and Moises 1982), while cholinomimetics usually show depressive or antimanic effects (Davis et al. 1978; Modestin et al. 1973). Concerning physiological differences, a reduction of the cholinergic modulated rapid eye movement (REM) sleep latency (Gillin et al. 1984) and an increased sensitivity to the induction of REM sleep by cholinomimetics has been shown in primary depressives (Sitaram et al. 1982; Berger et al. 1985). Sitaram et al. (1982) suggested that cholinergic supersensitivity is part of the genetic predisposition to affective disorders.

Both the cholinergic and adrenergic hypotheses of affective disorders suggest the possibility that the density of muscarinic and adrenergic receptors might be an underlying neurobiological cause of personality traits predisposing to depression. The aim of our exploratory study was to investigate possible relationships between personality traits known or suspected to play a role in the predisposition to depression and muscarinic and β-adrenergic receptors.

Methodologically, we chose erythrocytes and lymphocytes as muscarinic and β-adrenergic receptor models, since they are easily accessible, their receptor properties have been shown to correlate with those of other tissues in the same individual (Tollefson et al. 1982; Brodde et al. 1986), and they offer the possibility of differentiating subtypes of muscarinic receptors with a predominance of M1 receptors on erythrocytes and M2 receptors on lymphocytes (Bering and Müller 1987; Bering et al. 1987). In order to avoid biases resulting from disease and drug effects the study was carried out on healthy volunteers.

Subjects and Methods

Subjects. A total of 16 healthy volunteers (males, mean age 27.12 SD 3.72 years), all medical students at the University of Heidelberg, participated in the study. Informed consent was obtained after the nature of the investigation had been fully explained. Smoking and drinking habits, sport and physical activities, diseases, family history and psychopathology were evaluated in a standardized interview by an experienced psychiatrist. All subjects were free of concurrent diseases and drug-free according to their own information. None of the participants had a personal or familial history of mental disorders.

Psychological Trait Measures. For evaluation of personality traits the Premorbid Personality Inventory (PPI) by von Zerssen was used which includes scales for orderliness (Tellenbach's melancholic type), extraversion, neuroticism, frustration intolerance, motivation, schizoidea, and social desirability (Dietzfelbinger 1985). Furthermore, relevant scales from the Freiburger Personality Inventory (FPI) measuring depression, extraversion, neuroticism, spontaneous and reactive aggressiveness (Fahrenberg et al. 1978), and from the German version (Blaser and Gehring 1972) of the Minnesota Multiphasic Personality Inventory (MMPI, Hathaway and McKinley 1942–1967) measuring characteristics of patients with depression, mania, schizophrenia, and paranoia were included in the investigation. Because of the impreciseness of personality trait measurement it was desirable to have some redundancy in the scales used in an explorative study of this kind.

Materials. The l-quinuclidinyl (phenyl-4-^{3}H) benzilate (^{3}H-QNB, sp. act. about 35 Ci/mmol), 1-*N*-methyl-^{3}H) scopolamine methyl chloride (^{3}H-NMS, sp. act. 70 Ci/mmol), and l-propyl-2,3-^{3}H dihydroalprenolol (^{3}H-DHA, sp. act. 550 Ci/mmol) were obtained from Amersham-Buchler Braunschweig, FRG. All other drugs and chemicals were obtained from commercial suppliers.

Tissue Preparation. Heparinized blood was obtained from the healthy volunteers. The blood was diluted (1:1) with Hanks' balanced solution and centrifuged on a Ficoll-Paque gradient according to Boyum (1968), which also allowed the simultaneous isolation of lymphocytes from the same blood sample (Bering et al. 1987). Erythrocytes membranes were prepared according to Aronstam et al. (1977) with slight modifications

(Bering and Müller 1987). The erythrocyte layer was diluted with 10 volumes of ice-cold 10 mmol/l Tris-EDTA buffer pH 6.0, allowed to stand on ice for 30 min, and then centrifuged for 30 min at 30,000 *g* at 4°C. The resulting pellet was washed in about 20 volumes of the same buffer and centrifuged again. This procedure was repeated six times.

^{3}H-QNB Binding Assay to Erythrocyte Membranes. Erythrocyte membranes were resuspended in 50 mmol/l Tris-HCl buffer pH 7.4 (about 0.3 mg protein/ml). The final volume was similar to the original blood volume. Aliquots of the membrane (0.5 ml) suspension were incubated together with ^{3}H-QNB at 25°C for70 min. Each experiment was performed in triplicate. The incubation was terminated by filtration through Whatman GF-B glass fiber filters under slight vacuum. The filters were washed three times with 4 ml ice-cold incubation buffer. The radioactivity on the filter was extracted over 24 h at room temperature with 4 ml scintillation fluid (Quickszint 402, Zinsser, Frankfurt) and counted in a Beckman liquid scintillation counter (model LS 6800) at a counting efficiency of 43%. Saturation experiments were always carried out using 8 different concentrations of ^{3}H-QNB ranging from 2 to 20 nmol/l. Scatchard plots were analyzed by linear regression analysis. Nonspecific binding was always determined by parallel experiments in the presence of 100 µmol/l unlabeled atropine and accounted for about 70%–80% of total binding at low concentrations of ^{3}H-QNB (Bering and Müller 1987).

^{3}H-NMS Binding Assay to Lymphocytes. Aliquots (400 µl) of a lymphocyte suspension in phosphate-buffered saline (PBS) pH 7.6 were incubated with ^{3}H-NMS for 30 min at 20°C, after which time binding was in equilibrium (Bering et al. 1987). Each experiment was performed in triplicate. The incubation was terminated by rapid filtration through Whatman GF-C glass fiber filters under slight vacuum. The filters were washed three times with ice-cold PBS and dried for 30 min at 50°C. The radioactivity was extracted into scintillation fluid (Quickszint 402, Zinsser Frankfurt) over 24 h at room temperature and counted in a Beckmann liquid scintillation counter. Saturation experiments were carried out using 6 different concentrations of ^{3}H-NMS ranging from 2 to 12 nmol/l. Scatchard plots were analyzed by linear regression analysis. Nonspecific binding was always determined by parallel experiments in the presence of 100 µmol/l cold atropine and amounted to about 50%–60% of total binding at low concentrations of the radioligand.

^{3}H-DHA Binding Assay to Lymphocytes. A 400 µl sample of the lymphocyte suspension in PBS pH 7.8, additionally containing ascorbic acid 0.8 mmol/l, phentolamine 0.1 mmol/l, catechol 0.3 mmol/l, and chloroquine 50 µmol/l, was incubated with ^{3}H-DHA for 25 min at 20°C, after which time binding was in equilibrium. Each experiment was performed in triplicate. The incubation was terminated by rapid filtration through Whatman GF-C glass fiber filters under slight vacuum. All other steps were similar to the procedures described under the ^{3}H-NMS binding assay. Saturation experiments were carried out using 6 different ^{3}H-DHA concentrations ranging from 1 to 11 nmol/l. Scatchard plots were analyzed by linear regression analysis. Nonspecific binding was always determined by parallel experiments in the presence of cold (D,L) propanolol (10 µmol/l) and amounted to about 50% of total binding at low concentrations of the radioligand.

Statistical Analysis. The calculation of canonical correlations would be the ideal method for the analysis of relationships between two classes of variables such as personality and receptor variables in order to assess the correspondence between the basic dimensions of each set. However, to achieve stable results this method requires a larger number of subjects than was available for our exploratory study.

For this reason, our approach was to examine patterns of bivariate correlations between personality and receptor variables. Spearman rank correlation coefficients wre calculated and a two-tailed test of significance was used. In order to exclude the possibility that our findings were due to chance (Bonferroni inequality) each p value obtained was multiplied by the number of correlations calculated. Furthermore, a principal components factor analysis of all variables was carried out to place the bivariate results in a dimensional framework. The first three major factors that emerged from these analyses were rotated by the varimax method. For factor analysis a larger number of subjects is normally required. Thus the results of the factor analysis should be regarded with caution.

Results

Table 1 shows the means and SD of the variables under investigation. The calculation of Spearman's

Table 1. Means and SD of the quantitative variables under investigation

Variable	Mean	SD
Age	27.12	3.72
Alcohol consumption (ml/week)	55.12	39.70
Cigarettes per day	8.19	10.05
Sport activity (h/week)	9.15	22.23
Physical activity[a]	75.62	175.31
B max muscarinic receptors on lymphocytes[b]	38.65	80.30
B max β-adrenergic receptors on lymphocytes[b]	45.36	96.90
B max muscarinic receptors on erythrocytes[c]	107.99	219.61
FPI-depression	7.44	6.12
FPI-extraversion	11.25	5.88
FPI-neuroticism	8.06	5.23
FPI-spontaneous aggressiveness (2)	8.00	2.56
FPI-reactive aggressiveness/dominance (9)	5.56	3.01
MMPI-depression	20.69	7.04
MMPI-paranoia	8.19	3.75
MMPI-schizophrenia (k)	28.62	5.94
MMPI-hypomania (k)	20.12	6.38
PPI-extraversion	19.19	8.06
PPI-neuroticism	15.00	8.38
PPI-frustration intolerance	12.12	3.24
PPI-orderlines	10.00	11.23
PPI-schizoidea	11.87	5.40
PPI-social conformity	14.31	4.44
PPI-motivation	11.37	11.66

[a] hours in the previous month; [b] fmol/l $\times 10^6$ cells
[c] fmol/mg protein; (k) = K-corrected
FPI = Freiburger Personality Inventory
MMPI = Minnesota Multiphasic Personality Inventory (German version)
PPI = Premorbid Personality Inventory

correlation coefficients between the personality scales revealed that the orderliness scale from the PPI did not correlate significantly with other scales. The depression scales from the MMPI and the FPI did not intercorrelate significantly ($r = 0.39$). However, both depression scales correlated positively with neuroticism and negatively with extraversion scales; the MMPI depression scale showed a closer relationship to extraversion (FPI-E: $r = -0.57$, $P < 0.01$; FPI-N: $r = 0.45$, $P < 0.05$) whereas the depression scale from the FPI correlated more with neuroticism (FPI-N: $r = 0.78$; $P < 0.001$; FPI-E: $r = -0.05$, N.S.). The social desirability scale (PPI-SE) measuring dissimulation tendencies correlated significantly positively with paranoia ($r = 0.48$, $P < 0.05$) and motivation ($r = 0.51$, $P < 0.05$), and significantly negatively with PPI neuroticism (PPI-SU: $r = -0.69$, $P < 0.001$), schizoidea (PPI-SC: $r = -0.68$, $P < 0.01$), and the FPI spontaneous aggressiveness scale (FPI-2: -0.45).

Concerning the correlation coefficients between receptor density measurements, the densities of lymphocyte muscarinic and β-adrenergic receptors correlated highly significantly with each other ($r = 0.82$, $P < 0.001$) explaining 67% of the variance, whereas erythrocyte muscarinic receptor density showed no significant relationship with lymphocyte receptor densities. The erythrocyte density of muscarinic receptors correlated significantly positively with the amount of sport (estimated hours per week; $r = 0.47$; $P < 0.05$) and physical activity (estimated hours during the previous month; $r = 0.39$, $P < 0.05$) and significantly negatively with alcohol consumption ($r = -0.52$, $P < 0.05$). No significant correlations were obtained among confounding variables and lymphocyte receptor densities.

Table 2 presents the Spearman rank correlation coefficients between muscarinic and β-adrenergic receptor densities on blood cells and personality scales. In previous studies the erythrocyte muscarinic receptors showed characteristics of M1 receptors whereas lymphocyte muscarinic receptors those of M2 receptors (Bering and Müller 1987; Bering et al. 1987). The erythrocyte muscarinic receptor density correlated significantly positively with the reactive aggressiveness (dominance) scale on the FPI and the extraversion scale on the PPI and highly significantly negatively with the depression scale on the MMPI. The latter correlation explained 50% of the variance. On the other hand, the lymphocyte muscarinic receptor density correlated nonsignificantly positively with the orderliness scale on the PPI, a measure of Tellenbach's melancholic type. The lymphocyte β-adrenergic and muscarinic receptor densities showed the same pattern of correlations. Both correlated negatively with the spontaneous aggressiveness scale on the FPI, the β-adrenergic receptor density significantly and the muscarinic receptor nonsignificantly, and both correlated negatively with the extraversion scale on the FPI. Moreover, after the correction of Bonferroni inequality the negative correlation between the muscarinic receptor density on erythrocytes and the MMPI depression scale remained significant ($P < 0.05$).

Table 2. Spearman's correlation coefficients between receptor and personality measurements[a] ($N = 16$)

Personality scales	B max muscarinic receptors on erythrocytes (M1)	B max muscarinic receptors on lymphocytes (M2)	B max β-adrenergic receptors on lymphocytes
MMPI-depression	−71***·*	5	9
MMPI-hypomania (k)	18	11	−19
MMPI-paranoia	−25	−16	−11
MMPI-schizophrenia (k)	−24	24	24
FPI-depression	−5	10	−5
FPI-extraversion	25	−30	−38
FPI-neuroticism	−8	22	2
FPI-spontaneous aggressiveness	3	−39	−51**
FPI-reactive aggressiveness/dominance	48**	8	−15
PPI-orderlines	11	36	9
PPI-extraversion	46**	−19	−32
PPI-neuroticism	−17	28	32
PPI-frustration intolerance	9	23	4
PPI-schizoidea	−15	−31	−20
PPI-motivation	10	6	5
PPI-social conformity	−5	6	−13

[a] decimal points omitted; (k) = K-corrected; *** = $P < 0.001$ (two-tailed); ** = $P < 0.05$ (two-tailed); * = $P < 0.05$ after the correction of Bonferroni inequality

To control for the significant confounding variables on the significant correlations among erythrocyte muscarinic receptor density (M1), depression (MMPI), reactive aggressiveness (FPI), and extraversion (PPI) partial correlations were calculated. The magnitude of the correlation coefficient between the depression scale (MMPI-D) and the erythrocyte receptor density (M1) was not reduced by this procedure. The magnitude of the correlation coefficient between the erythrocyte receptor density (M1) and the reactive aggressiveness scale (FPI-7) decreased slightly by 27% for alcohol consumption and sport activity. Furthermore, a slight reduction of about 20% was observed for the correlation between erythrocyte muscarinic density (M1) and extraversion

Table 3. Factor loadings[a] derived from principal components analysis modified by varimax rotation with loadings 30 set to

	Factor 1	Factor 2	Factor 3
PPI-neuroticism	92	–	–
FPI-neuroticism	84	–	–
FPI-depression	84	–	–
PPI-social desirability	–58	–	–
MMPI-paranoia	–33	–	–
PPI-extraversion	–	73	–
FPI-reactive aggresiveness/ dominance	–	54	–
MMPI-schizophrenia	–	–74	–
PPI-motivation	–	–	65
FPI-spontaneous aggressiveness	37	–	–84
PPI-schizoidea	74	–	–36
MMPI-depression	48	–59	–
FPI-extraversion	–	67	–45
PPI-orderliness	–	65	36
MMPI-hypomania	–	31	–34
PPI-frustration intolerance	–	–	–
Lymphocyte β-adrenergic receptors	–	–	59
Lymphocyte muscarinic receptors (M2)	–	–	49
Erythrocyte muscarinic receptors (M1)	–	54	–

[a] decimal points omitted

(PPI-E) by sport and physical activities. In summary, the confounding variables could not explain the major part of the significant correlations between personality scales and receptor densities.

Factor analysis was used to better visualize the relationships among receptor and personality variables. The first three major factors that emerged from this analysis were rotated. Factor loadings (except those below 0.3) are shown in Table 3. Factor I was defined by neuroticism scales and the depression scale from the FPI on the positive pole, and the PPI social desirability scale at the negative pole. This factor seemed to represent the neuroticism factor. Receptor variables did not load on the neuroticism factor. Factor II was defined at the positive pole by extraversion scales and the FPI reactive aggressiveness (dominance) scale, and at the negative end by the schizophrenia and depression scale from the MMPI. Factor II seemed to be identifiable as an extraversion factor. The erythrocyte muscarinic receptor density (mainly M1) loaded on the extraversion factor. Factor III was identified on the positive pole by the motivation scale from the PPI and at the negative end by the FPI spontaneous aggressiveness scale. Factor III was labeled lack of spontaneous agressiveness factor. Lymphocyte β-adrenergic and muscarinic receptor (mainly M2) densities loaded on this aggressiveness factor.

Discussion

The discussion of the results will be divided into four parts: (1) the first presents a brief review of the principal findings, (2) in the second an attempt is made to eliminate chance or confounding variables as an explanation of the findings, (3) in this part the literature concerning the biological basis of personality and depression will be discussed with regard to agreement or disagreement with our results, and (4) in conclusion the findings of the present study indicate a relationship between personality predisposition factors and neurobiological predisposition factors to depressions.

(1) Lymphocyte muscarinic and β-adrenergic receptors densities intercorrelated highly significantly. Furthermore, the results presented reveal significant relationships between muscarinic and β-adrenergic receptor densities on blood cells and personality measurements of depressives such as depression, introversion, and aggressiveness. With regard to personality factors, erythrocyte muscarinic receptor density correlated highly significantly negatively with depression on the MMPI and significantly positively with reactive aggressiveness (dominance) on the FPI and extraversion on the PPI (Table 2). The β-adrenoceptor density on lymphocytes correlated significantly negatively with spontaneous aggressiveness, a scale on which premorbid unipolar depressives scored significantly higher (Angst and Clayton 1986).

(2) Can the effect of chance or confounding variables explain the observed significant correlations between receptor and personality measures? First, removing the significant confounding variables in the correlations most likely to be influenced revealed no major change in the results, indicating that the significant correlations between personality and receptor variables were probably not caused by confounding variables. However, since it is impossible to control for all variables this possibility can never be completely ruled out. Second, of the 48 correlations between receptor and personality measures, 4 were significant at least at the 0.05 level. As approximately 2 correlations might have been expected by chance, the results suggest that something more than chance was operating. Third, the pattern of correlations – same direction of correlations for extraversion, neuroticism,

and depression scales from different questionnaires and for lymphocyte β-adrenergic and muscarinic receptors which in turn intercorrelated – suggested systematic relationships between related variables rather than random ones. Fourth, after the correction of Bonferroni inequality the correlation between the MMPI depression scale and erythrocyte muscarinic receptor density remained significant. Thus chance or confounding variables were unlikely candidates for explaining the observed receptor-personality relationships.

In conclusion, the results of the present study confirm the postulated relationship between receptor densities and personality traits of depression-prone individuals since muscarinic and β-adrenergic receptor densities correlated significantly with depression, introversion, and aggressiveness. However, the pattern of correlations was more complex than expected. Factor analysis enabled us to simplify somewhat the complex picture of the bivariate correlations. The first three factors that emerged were identified as neuroticism, extraversion, and lack of spontaneous aggressiveness factor (Table 3). Neuroticism, either as scale or as factor, did not show any relationship with receptor densities. The extraversion factor seemed to be related to erythrocyte muscarinic receptor density (M1) in contrast to β-adrenergic receptors densities which showed a relationship to the third factor covering spontaneous aggressiveness. The significant positive correlations among erythrocyte muscarinic receptor density, reactive aggressiveness (dominance), and extraversion on the PPI and the significant negative correlation with depression on the MMPI might be explained by their loadings on the extraversion factor (Table 3). Thus the significant bivariate correlations between personality scales and receptor densities might be explained by two personality factors, extraversion and spontaneous aggreesiveness. However, since for factor analysis larger number of subjects are normally required, the results of our factor analysis must be regarded with caution.

(3) In the following part, the literature on personality, neurobiology and depression will be examined with regard to agreement or disagreement with the results of the present study. The discussion rests on two unproven assumptions. It is assumed that receptor densities exert an effect on personality factors, although correlations clearly do not indicate the direction of cause and effect. Moreover, muscarinic and β-adrenergic receptor densities on different cell types such as erythrocytes, lymphocytes, and neurons of the brain are thought to be related. Some evidence in favor of this latter assumption is based on the finding of a highly significant linear relation between β-adrenoceptor density of lymphocytes and on the corresponding myocard cells from the same individual (Brodde et al. 1986).

How are the results of the present study related to the findings of others concerning personality? Using the same research strategy employed in this study a significantly negative correlation between the MMPI depression scale and urinary phenylethylamine has been found (Moises et al. 1986). However, to our knowledge no comparable data have been published concerning personality traits and muscarinic and β-adrenergic receptor densities. Our finding of a positive relationship between erythrocyte muscarinic receptor density (M1) and reactive aggressiveness (dominance) is in agreement with the results of animal studies. Generally, it has been demonstrated in animals that cholinergic agonists facilitate or induce aggression, while atropinics block aggressive behavior as well as aggression induced by acetylcholine or cholinomimetic agonists (Myers 1974; Allikmets 1974; Wahlen and Simon 1984).

How do the results of the present study agree with receptor studies in psychiatric patients? Since premorbid major depressives scored higher on spontaneous agressiveness (Angst and Clayton 1986) our finding of a significantly inverse correlation between spontaneous aggressiveness and β-adrenergic receptor density is in agreement with the catecholaminergic deficiency hypothesis of depression (Schildkraut 1965; Bunney and Davis 1965; Matussek 1966) and with results from the literature. The majority of studies found descreased β-adrenoceptor densities in depressive patients (Wright et al. 1984; Extein et al. 1979; Mann et al. 1985; Wood et al. 1986) with the exception of Healy et al. (1983) who reported elevated β-adrenergic receptor densities on lymphocytes of depressive patients. Our results seem to be a variance with Sulser's noradrenergic hypersensitivity hypothesis of depression (Sulser et al. 1978) which has been criticized elsewhere (Waldmeier 1981).

With regard to muscarinic receptors, our findings of a significantly inverse correlation between the MMPI depression scale and the muscarinic receptor density on erythrocytes (mainly M1 receptors) and the positive correlation with extraversion predicts reduced M1-muscarinic receptor densities in depressive patients since depressives scored higher on the depression scale of the MMPI and on introversion scales (Hathaway and McKinley 1942–1967; Kendell and Discipio 1968; Paykel et al. 1976; Frey 1977; Hirschfeld 1986). Obviously, this would not be in agreement with the cholinergic supersensitivity hypothesis of genetic predisposition to depression of Sitaram et al. (1982). Sitaram's hypothesis is able to explain the findings of reduced cholinergic modulated REM

sleep latency and of an increased sensitivity to the induction of REM sleep by cholinomimetics in primary depressives (Sitaram et al. 1982; Gillin et al. 1984; Berger et al. 1985) and the results of Nadi et al. (1984). It is unknown, however, whether the muscarinic receptors responsible for the induction of REM sleep correspond to erythrocyte (M1) or lymphocyte (M2) muscarinic receptors. Furthermore, the discrepancy between the results of our study and the cholinergic supersensitivity hypothesis is based on the assumption that the depression scale of the MMPI could be employed as a measure of predisposition to endogenous depressions. It seems likely that the MMPI depression scale is a better measure for predisposition to neurotic than endogenous depression since it is known that neurotic depressives score higher on neuroticism and introversion and in our study the depression scale from the MMPI correlated significantly with neuroticism and extraversion scales. On the other hand, endogenous depressives score higher only on itroversion (Kendell and Discipio 1968; Paykel et al. 1976; Frey 1977; Hirschfeld 1986).

Concerning the findings of Nadi et al. (1984) it should be noted that other investigators were unable to identify muscarinic receptors on fibroblasts stimulating a controversy about the usefulness of cultured skin fibroblasts as a model for muscarinic receptors (Lenox et al. 1985; Kelsoe et al. 1985; Gershon et al. 1985).

(4) Which conclusions for the etiology of depression might be drawn from the present findings? Clearly, the results of the present study indicate a relationship between personality factors predisposing to depression and muscarinic and β-adrenergic receptor densities on blood cells in contrast to a lack of significant correlations with personality factors designed to measure predisposition for schizophrenia. As far as M1-muscarinic receptors are concerned, a decrease in muscarinic receptor density might play a role in the predisposition to neurotic, reactive, or minor depressions. With regard to β-adrenoceptors, the findings of Angst and Clayton (1986) in combination with our results suggest a premorbid decrease in β-adrenergic receptor density in major depression.

Finally, since all our subjects were clinically depression-free, it is obvious that reductions in M1-muscarinic of β-adrenergic densities are not a sufficient and – considering the heterogeneous nature of symptomatic depressions – even not a necessary cause of depression. For this reason, it is tempting to speculate about the possible relationships of muscarinic and β-adrenergic receptors to more crucial and additional variables in the pathogenesis of depressions. For example, acute stress induces increased utilization and synthesis or noradrenaline, whereas chronic uncontrollable stress results in depletion of noradrenaline, dopamine, serotonin, and an increase in acetylcholine (Anisman 1984). Furthermore, life experiences, social, personality, and hereditary factors may contribute to an individual's ability to control stress.

In summary, M1-muscarinic and β-adrenergic receptor densities are related to premorbid personality traits of depressive patients. This finding suggests the participation of neurobiological factors in the development of personality traits predisposing to depression. However, neither decreased M1-muscarinic and β-adrenergic densities – within the ranges of this study – nor personality factors are apparently a sufficient or necessary cause of depression. More essential or additional factors are required to explain the development of depression. These additional biological or psychological factors might interact with the predisposition factors investigated in this study in a yet unknown way to cause depression.

Further studies in normals with larger samples including both sexes and wider ranges of the personality variables aggressiveness, depression, extraversion, and orderliness, investigations of the relation between muscarinic and β-adrenergic receptor densities on blood cells and central neurons, the control of relevant personality factors in receptor studies comparing patients with controls, and longitudinal studies of receptor densities in affective patients are required before reliable conclusions for the pathogenesis of affective disorders can be drawn.

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