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S. Braune · M. Albus · M. Fröhler · T. Höhn · G. Scheibe

# Psychophysiological and biochemical changes in patients with panic attacks in a defined situational arousal

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**Summary** A group of 27 patients with panic disorder with or without agoraphobia were compared with 10 control subjects before stress exposure. No statistically significant differences between patients and controls were found for the cardiovascular parameters. Skin conductance level and skin conductance reaction were significantly higher in the patient group. They also showed higher self-ratings in behavioural symptoms associated with anxiety. There were statistically significant higher venous plasma levels of norepinephrine in patients than in controls, although the epinephrine levels were similar. The number of binding sites of $\alpha_2$-receptors and the affinity of $^3$H-yohimbine to the α2-receptors on intact thrombocytes was statistically significantly lower in patients compared to controls. Significant differences between the gender groups of patients and controls were found for electrodermal activity and epinephrine levels. These data add further evidence to an overshooting activation of the noradrenergic pathway in patients with panic disorder, possibly based on a dysregulation of $\alpha_2$-receptor.

**Key words** Panic disorder · Stress · α-2-receptors Catecholamines · Psychophysiology

S. Braune
Department of Neurology, Hospital of the University of Freiburg, Hansastr. 9, D-79104 Freiburg, Germany

M. Albus (✉)
State Mental Hospital Haar, Vockestr. 72, D-85529 Haar, Germany

M. Fröhler
BMW AG, Petuelring 130, D-80809 München, Germany

T. Höhn
Department of Paediatrics, Hospital of the University of Freiburg, Hugstetterstr. D-79106 Freiburg, Germany

G. Scheibe
Department of Psychotherapy, University of Düsseldorf, Moorenstr. 5, D-40225 Düsseldorf, Germany

## Introduction

For several decades many attempts have been made to understand the pathophysiological mechanisms of anxiety disorders. Higher electrodermal activity at baseline (Bond et al. 1974; Roth et al. 1986), higher rates of spontaneous fluctuations of skin-conductance reaction (Hart 1974; Roth et al. 1986) as well as higher heart rate at baseline (Freedman et al. 1984; Nesse et al. 1985; Yeragani et al. 1989) in anxiety patients have been reported from psychophysiological investigations. These findings have been considered supportive of the hypothesis of higher sympathetic arousal in anxiety patients.

Besides psychophysiological investigations findings of drug challenges with substances with a known action in the central nervous system (CNS), such as the $\alpha_2$-adrenoceptor antagonist yohimbine (Charney et al. 1984, 1987, 1992; Uhde et al. 1985; Albus et al. 1992) and the $\alpha_2$-adrenoceptor agonist clonidine (Charney and Heninger 1986; Charney et al. 1992; Uhde 1989) led to the hypothesis that panic attacks are triggered by an impaired presynaptic regulation of the release of norepinephrine (NE) in the locus coeruleus (Charney et al. 1984, 1987, 1992). In addition, reports of significantly lower density of platelet $\alpha_2$-receptors (Cameron et al. 1984, 1990; Bondy et al. 1988), with no differences in affinity with $^3$H-yohimbine as a ligand point in potential alterations in the sensitivity or density of the receptor in panic patients. Together these results provide evidence for a potential hyperreactivity of noradrenergic neuronal CNS pathways in pathological anxiety, as had already been suggested by Nesse et al. (1984) and Villacres et al. (1987), based on findings of an enhanced level of autonomic and catecholaminergic activation in patients with panic disorder.

The results are not unequivocal, however, indicating a core problem of psychophysiological assessments: the highly variable covariation between psychological, physiological and biochemical parameters, which are strongly influenced by the type and specificity of the test situation, and the interpersonal variability of the autonomic re-

sponse (Lacey 1967; Albus et al. 1986; Albus 1987, 1990; Robinson et al. 1987). It appears that the degree of arousal at baseline plays a significant role in terms of behavioural sensitivity. Moreover, experimental design has been shown to affect the response to anxiogenic agents in several studies (van der Molen et al. 1987; Sanderson et al. 1989; Albus et al. 1992). Because it is well known that different situations elicit different responses in patients and controls we tried to parallel the anxiety-inducing properties of the test situation.

In contrast to drug-challenge studies in which patients anticipated receiving an anxiogenic drug, we chose a situation in which patients and controls expected to have to cope with different stressors. This expectancy situation differs also with regard to coping mechanisms compared to drug-challenge studies. Whereas in challenge studies patients knew that they would be confronted with the anxiogenic effects of a drug that they would have to tolerate passively, expectation of neutral stressors such as mental arithmetic can be considered a situation that has to be coped with actively. Because anxiety and stress induce similar autonomic activation expectancy of stress exposure, which has already been shown to be stressful for healthy controls (Albus 1987), was introduced to assess differences between patients and controls in a state of higher arousal.

The purpose of the study was to compare $\alpha_2$-adrenoceptors on intact thrombocytes, plasma levels of catecholamines, physiological parameters and rated anxiety in patients with panic disorder according to DSM-III-R criteria with controls. A test situation that was characterised by anticipatory anxiety was chosen because it: (1) represents a typical state of mood in patients with panic disorders and (2) contributes to a delimitation of the interpersonal variability of the parameters assessed by the induction of a standardised situational arousal.

## Patients and methods

A group of 27 patients who met DSM-III-R criteria for panic disorder with (12 patients) and without (15 patients) agoraphobia were compared with 10 normal controls. All patients sought treatment at the outpatient department of the Psychiatric Clinic of the University of Munich. They had either been referred to the clinic by a practitioner or had read about this investigation in a newspaper article. The patients had been off any psychoactive medication for at least 3 weeks before entering the study. Before the washing out period two patients had been on tricyclic antidepressants over a period of 3 weeks, and seven patients were treated with benzodiazepines ad lib. with a maximum dosage of an equivalent of 5 mg diazepam per day. Mean age, age range, sex distribution, previous medication and psychopatholgoical parameters are given in Table 1. Comprehensive physical and psychiatric examination, ECG and blood tests were performed. Each subject was informed in detail about the investigation and gave consent. Most patients seeking advice were highly motivated and only three patients (age 25, 39 and 43 years) who fulfilled the inclusion criteria refused to participate.

### Healthy subjects

A total of four male and six female healthy volunteers (mean age 37.1 years; range 23–50 years) participated in this study as controls. Their results of the physical examination, ECG and blood tests were within normal limits, and none of them had a history of a psychiatric or serious medical disorder. They underwent a semi-structured interview covering drug and/or alcohol abuse, personality disorders, mood and obsessive-compulsive disorders as well as psychotic disorders. They all gave informed consent.

### Experimental setting

The investigation was conducted in a quiet, well-lit room between 8 and 11 a.m. Subjects were seated in a comfortable chair, providing easy access to the i.v cannula in a forearm vein, which was kept patent with a standard saline solution and allowed the subject to fill in the rating scales. The subjects knew that they would undergo various stressor experiments after this initial resting period, including mental arithmetic with a strict time limitation, preparation and delivery of a speech to be recorded by a microphone on the topic of contraceptives and the presentation of a video with adverse contents. After completion of all preparations 15 min later the blood samples were drawn from the cannula and each patient assessed his/her subjective feelings on a visual analogue scale (VAS).

### Physiological parameters

Heart rate (HR) and electrodermal activity (EDA) were measured continously on-line with a polygraph via skin electrodes on the chest and the palm of the left hand. Blood pressure (BP) was assessed automatically each minute by an infraton tensiomat (model FIB 20, Boucke GmbH, Tübingen), employing the Riva–Rocci–Korotkoff method. The results used for analysis are the mean values over the last 3 min of the 15-min test time.

**Table 1** Demographical and psychopathological characteristics of patients with anxiety disorders. STAI State-Trait Anxiety Inventory: X1 = state, X2 = trait; HAMA/HAMD Hamilton Anxiety/Depression Scale)

| Parameter | Patients ($n$ = 27) |
|---|---|
| Diagnosis panic disorder | 12 |
| Diagnosis panic disorder and agoraphobia | 15 |
| Mean age (years) | 37.7 ± 7.3 |
| Age range (years) | 22–51 |
| Sex: Male | 11 |
| Female | 16 |
| Mean duration of illness (years) | 7.14 ± 5.9 |
| Mean number of panic attacks per week | 2.5 ± 2.8 |
| Pretreatment with: | |
| No medication | 12 |
| Benzodiazepines | 7 |
| Beta-blockers | 5 |
| Antidepressants | 2 |
| Neuroleptics | 1 |
| STAI X1 (mean) | 53.1 ± 11.8 |
| STAI X2 (mean) | 54.1 ± 8.4 |
| HAMA (mean) | 17.7 ± 3.6 |
| HAMD (mean) | 13.0 ± 3.1 |

Subjective self-assessment

A VAS was used for subjective self-rating at the end of this anticipatory anxiety-inducing situation. The scale consisted of four cognitive (panicky feelings, anxiety, nervousness and aggressiveness) and four physical (muscle tension, fatigue, perspiration and feeling of heart beating) characteristics. Each subject was asked to mark his/her level of feeling for each item between the two possible extremes: *none* on the left- and *extreme* on the right-end of a 100-mm line. The distance in mm from the left-hand side was taken as measurement for the analysis.

Biochemical methods

*Blood collection*

Fresh blood was collected (50 ml) for the determination of $\alpha_2$-adrenoceptors in plastic tubes containing ethylenediaminetetraceticacid (EDTA) (20 mM) as an anticoagulant. Blood for the catecholamine (CA) determination was collected (20 ml) with NH4-heparin (7.5 IE/ml) as an anticoagulant and reduced gluthathion (4 mM) as an antioxidation factor.

*Cell preparation and radioreceptor binding assay*

The fresh blood was centrifuged at room temperature (400 g/10 min), separating the platelet-rich plasma. Platelets were washed in Hank's salt solution containing EDTA (5 mM; pH = 7.2). Platelet counts were done by means of a Ultra-Flow 100 (Clay-Adams, Becton & Dickinson, Heidelberg). The radioreceptor binding assay using intact platelets was performed immediately after platelet separation with a slight modification (Motulsky et al. 1980; Daiguji et al. 1981).

The following is the assay in detail: intact platelets, labeling agent $^3$H-yohimbine, specific activity 70–90 CI/mMol, concentration range 0.1–5 nM; displacing agent 0.1 mM L-norepinephrine; 0.1 mM brenzcatechine; incubation buffer Tris-HCL (50 mM), NaCl (20 mM), KCL (5 mM), pH = 7.0; incubation time and temperature (60 min, –25° C).

The reaction was stopped by high-speed centrifugation (10,000 g/5 min), the supernatant was carefully removed and the pellets were solubilised with 0.5 ml Protosol (tissue solubiliser; New England Nuclear [NEN], Dupont, Bad Homburg). The solubilised material was then transferred into scintillation vials, and 50 ml glacial acid an 10 ml Econofluor (NEN) was added. Radioactivity was determined in a Searly Mark III (Zinsser, Frankfurt) scintillation counter. Buffer blanks were included in all assays. All data points were performed in duplicate, with the variation coefficient between duplicates being less than 10%. A total of ten concentrations were used in the saturation experiments; at least seven were used to calculate the binding parameter $B_{MAX}$ and $K_D$ (Scatchard 1949; Rosenthal 1967).

*Catecholamine determination*

Circulating CA in serum was determined with high-performance liquid chromatography (HPLC-ECD) (Ackenheil et al. 1982). In summary, the plasma samples were purified and concentrated by extraction with aluminia prior to chromatography. The HPLC-electrochemical detection (ECD) system used a cation exchange column (Nucleosil 5 SA (Macherey & Nagel, Düren), mobil-phase sodium acetate/citric acid buffer, pH = 5.2; flow rate 0.8 ml/min, 1500 PSI) coupled with a glass carbon-electrode detector cell, potential +0.72 V vs Ag/AgCl reference electrode, sensitivity 0.1–0.5 nA, full scale.

Data analysis

To evaluate differences between patients and controls as well as between genders analysis of variance (ANOVA) with two group factors (patients vs controls and males vs females) were carried out for the parameters investigated. To evaluate correlations between physiological, biochemical and subjective parameters a Pearson rank-correlation was carried out.

## Results

### Physiological parameters

No significant differences between patients and controls (Table 2) as well as between genders (not shown) were found for the cardiovascular parameters, namely HR and systolic and diastolic BP.

Patients showed significantly higher skin-conductance levels (SCLs; $df = 1;36$; $F = 3.46$; $P < 0.05$; with Huyn-Feldt-ε-correction, $\varepsilon = 0.5547$) and skin-conductance reactions (SCRs) ($df = 1;36$; $F = 3.88$; $P < 0.05$) compared with healthy controls (Table 3).

Whereas the SCL of the male group was significantly higher then in the male control group ($df = 1;16$; $F = 5.24$; $P < 0.05$), the female patients showed a significantly higher SCR compared to their healthy controls ($df = 1;21$; $F = 4.19$; $P < 0.05$; Table 3).

**Table 2** Mean and SD for heart rate (HR, beats/min) and blood pressure (BP, mmHg; syst. systolic; diast. diastolic) in patients with panic attacks and controls

| | | HR | BP (syst.) | BP (diast.) |
|---|---|---|---|---|
| Patients ($n = 27$) | Mean | 78.92 | 120.43 | 79.35 |
| | SD | 13.19 | 15.80 | 9.45 |
| Controls ($n = 10$) | Mean | 75.65 | 112.50 | 74.50 |
| | SD | 8.50 | 13.17 | 11.60 |

**Table 3** Mean and SD for skin-conductance level (μS/cm$^2$; SCL) and skin-conductance reaction (μS/cm$^2$; SCR) in patients with panic attacks and controls, as well as their gender subgroups. * $P < 0.05$

| All subjects | SCL | SCR |
|---|---|---|
| Patients ($n = 27$) | 14,370.83* ± 9,094.58 | 302.18* ± 287.51 |
| Controls ($n = 10$) | 9,572.65* ± 5,793.44 | 131.39* ± 168.44 |
| Gender subgroups: | | |
| Patients male ($n = 11$) | 18,355.25* ± 10,235.10 | 348.45 ± 208.34 |
| Controls male ($n = 4$) | 9,415.45* ± 6,709.64 | 180.06 ± 215.27 |
| Patients female ($n = 16$) | 11,935.27 ± 5,395.67 | 296.68* ± 338.68 |
| Controls female ($n = 6$) | 9,769.15 ± 5,420.82 | 70.56* ± 70.32 |

**Table 4** Mean and SD of the ratings of the cognitive and physical items of the Visual Analogue Scale with a range from 0–100 in patients with panic attacks and controls, and the results of statistical analysis by analysis of variance (ANOVA) between the two groups

| | Patients | Controls | ANOVA |
|---|---|---|---|
| Cognitive parameters | | | |
| Panicky feeling | 26.63 ± 25.76 | 9.30 ± 11.30 | $dF = 1, 37$; $F = 4.58$; $P < 0.05$ |
| Anxiety | 36.04 ± 24.90 | 9.80 ± 11.30 | $dF = 1, 37$; $F = 11.73$; $P < 0.01$ |
| Nervousness | 44.74 ± 21.04 | 25.10 ± 20.69 | $dF = 1, 37$; $F = 6.73$; $P < 0.05$ |
| Aggressiveness | 13.17 ± 18.00 | 6.47 ± 6.47 | n.s. |
| Physical parameters | | | |
| Muscle tension | 27.41 ± 23.07 | 11.22 ± 10.38 | $dF = 1, 37$; $F = 4.35$; $P < 0.05$ |
| Fatigue | 23.30 ± 19.44 | 5.56 ± 4.49 | $dF = 1, 37$; $F = 7.37$; $P < 0.01$ |
| Perspiration | 24.19 ± 20.59 | 26.60 ± 25.93 | n.s. |
| Heart beating | 24.85 ± 20.83 | 17.50 ± 15.65 | n.s. |

**Table 5** Mean and SD of venous plasma levels of norepinephrine and epinephrine in pg/ml in patients with panic attacks and controls, as well as their gender subgroups. ** $P < 0.01$; * $P < 0.05$

| All subjects | Norepinephrine | Epinephrine |
|---|---|---|
| Patients ($n = 23$) | 328.35** ± 88.90 | 54.78 ± 30.89 |
| Controls ($n = 10$) | 235.70** ± 53.05 | 59.70 ± 28.87 |
| Gender subgroups: | | |
| Patients male ($n = 11$) | 333.45 ± 89.26 | 75.27* ± 27.64 |
| Patients female ($n = 16$) | 322.13 ± 84.45 | 40.94* ± 21.83 |
| Controls male ($n = 5$) | 236.40 ± 52.68 | 62.00 ± 37.28 |
| Controls female ($n = 5$) | 235.00 ± 59.62 | 57.40 ± 21.73 |

**Table 6** Mean and SD for density ($B_{MAX}$) (molecules/cell) and affinity ($K_D$; n$M$) of $\alpha_2$-adrenoceptors in anxiety patients and controls. * $P < 0.05$

| $\alpha_2$-receptor | Density ($B_{max}$)* | Affinity ($K_D$)* |
|---|---|---|
| Patients ($n = 18$) | 228.72 ± 50.33 | 1.65 ± 0.50 |
| Controls ($n = 10$) | 287.40 ± 87.44 | 1.13 ± 0.46 |

Psychological parameters

Patients gave higher ratings for all items with the exception of perspiration. These differences were statistically significant for panicky feelings, anxiety, nervousness, muscle tension and fatigue (Table 4). No significant differences between genders were found.

*Biochemical parameters*

Venous plasma levels of NE were statistically significantly higher in patients with panic disorders than in the control group ($df = 1.37$; $F = 8.17$; $P < 0.01$). The epinephrine (E) levels showed no significant differences (Table 5).

Whereas the NE levels showed no statistical differences for the gender groups, the E level of the male patients was significantly higher ($df = 1;16$; $F = 9.41$; $P < 0.05$) than for the female patients (Table 5).

The density of the $\alpha_2$-receptors and the affinity of $^3$H-yohimbine to the $\alpha_2$-adrenoceptors was significantly lower in the anxiety patients compared to the controls ($B_{MAX}$: $df = 1;28$; $F = 4.40$; $P < 0.05$; $K_D$: $df = 1;28$; $F = 5.67$; $P < 0.05$) (Table 6). There were no statistically significant differences between genders.

Pearson rank-correlations showed within patients and controls significant correlations between panicky feelings, anxiety, aggressiveness, nervousness and muscle tension ($r$ ranging from 0.5969–0.8820; $P$ ranging from < 0.01–< 0.001). In healthy subjects a significant correlation between $\alpha_2$-receptor density and anxiety ($r = 0.7418$; $P < 0.01$) and also panicky feelings ($r = 0.6968$; $P < 0.01$) was found. Also, the $\alpha_2$-receptor affinity in this group was significantly related to anxiety ($r = 0.5988$; $P < 0.03$). In contrast, no such relationships were found in the patient group for these parameters. In none of the biochemical parameters did we obtain a statistically significant interaction between group and gender.

## Discussion

The patients with panic and phobic disorders responded to the test situation with more pronounced adverse feelings compared to the healthy controls. The statistically significant higher ratings of the items linked to anxiety such as panicky feelings, anxiety, nervousness, muscle tension and fatigue are in concordance with self-assessments of patients prior to drug or $CO_2$ challenges (Charney et al. 1984, 1986, 1992; Nesse et al. 1984; Woods et al. 1988; Albus et al. 1992). It underlines the phenomenon of high-expectation anxiety in these patients, as was also shown in an experiment on the psychological induction of panic in panic patients (Rachman et al. 1988). The statistically higher levels of SCR and SCL mirror this increased arousal in the autonomous response also, which is in line with other studies (Lader and Wing 1966; Bond et al. 1974; Freedman et al. 1984; Roth et al. 1986; Cowley et al. 1987). The differences in SCL and SCR between male and female patients and their controls, respectively, have not yet been described in the literature.

Further research with groups greater than in this study are necessary to validate these findings. As the cardiovascular parameters fail to demonstrate a difference, which was also found in the preadministration period of most drug-challenge trials (Charney et al. 1984, 1992; Charney

and Heninger 1986; Gaffney et al. 1988; Albus et al. 1992), this gross EDA activation emphasises the sensitivity of this reaction to stress-induced arousal in anxiety patients. This indicates a specific relation of the EDA to anxiety disorders exceeding the general physiological activation and orientation reaction, as was previously related to in healthy subjects (Fahrenberg 1979; Albus et al. 1986; Albus 1987).

Concerning hormonal activation we found statistically significant higher plasma levels of NE in anxiety patients than in healthy controls, as was also found in previous studies without defined exposure to stressors (Wyatt et al. 1971; Mathew et al. 1981; Ballenger et al. 1984). Interestingly, in the drug challenge investigations previously mentioned the baseline levels of NE (Nesse et al. 1984; Gaffney et al. 1988) or its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG; Charney et al. 1984; Charney and Heninger 1986) were not significantly elevated in patients, despite the high subjective anxiety ratings. A possible explanation could be that the patients expected to have to cope passively with the administered drug, in contrast to the active response necessary on exposure to experimental stressors in our setting. This dependency of hormonal activation on the type of stressor was also found in healthy volunteers (Mason et al. 1976; Erdmann et al. 1984). There appeared to be no differences between the genders.

The plasma levels of the other adrenal hormone E did not differ between groups. This replicates results from other studies in anxiety patients (Kralik et al. 1982; Gasic et al. 1985; Gaffney et al. 1988; Papp et al. 1988). However, higher E levels have also been reported in anxiety patients under several different experimental conditions (Mathew et al. 1981; Nesse et al. 1984; Villacres et al. 1987). Besides methodological incongruities a sex difference in the release of E under stress might be relevant. It has been reported that the MHPG excretion in urine of healthy women after stress exposure (Frankenhäuser et al. 1972; Johansson 1972; Johansson and Post 1974) and the E plasma levels in women with panic disorders expecting a lactate infusion (Papp et al. 1988) are significantly lower compared to male patients. This gender difference was also statistically significant in our patient population. Whether this fact is related to the lower EDA in female patients with panic disorders compared to male patients remains to be clarified.

The number of $\alpha_2$-receptors on intact thrombocytes in patients was statistically lower than in controls. The affinity to the ligand $^3$H-yohimbine was significantly lower in the patient group. No statistically significant differences between the genders of either group were found. Cameron et al. (1984) found lower receptor numbers on isolated membranes and no differences in affinity. This group used tritiated yohimbine in anxiety patients, however, in a setting without stressors. A change in affinity to an agonistic ligand could mean a change in the ratio of high- and low-affinity receptor-binding components as it is to be expected during desensitisation in β- (Waldo et al. 1983; Toews et al. 1984) and in α-receptors (Perry and U'Pritchard 1984). Nevertheless, the unequivocal lower numbers of receptors on membranes *and* on intact cells measured with $^3$H-yohimbine with and without exposure to stressors might point to a permanent change with either reduction in numbers or dysfunction of $\alpha_2$-receptors in anxiety disorders. Uhde et al. (1985), using the agonist $^3$H-dihydroergocryptine, and Norman et al. (1987), using the antagonist $^3$H-rauwolscine, reported higher numbers of binding sites in patients than in controls. The different types of ligands may explain these differences, and the influence of the circadian rhythm of these receptor parameters also cannot be ruled out (Fröhler et al. 1985, 1986).

If it is assumed that the mechanisms of hormone–receptor interactions are similar in all tissues of the body, as it was postulated for receptor desensitisation (Sibley and Lefkowitz 1985), and that therefore receptors on peripheral cells provide a valid model for receptor function on CNS neurons, our findings might allow a hypothesis on neuronal mechanisms in the CNS of anxiety patients. The lowered numbers of the mainly presynaptically located $\alpha_2$-autoreceptors on noradrenergic neurons could possibly be insufficient to inhibit NE release following a peripheral stimulus. This is supported by results from drug-challenge investigations with the central active $\alpha_2$-receptor antagonist yohimbine (Charney et al. 1984) and the agonist clonidine (Charney and Heninger 1986), which showed a more pronounced NE activation. This was accompanied by a higher increase in anxiety feelings in patients compared to healthy controls after the administration of these drugs, also suggesting a dysfunction of this receptor. Neuroanatomically a high proportion of α-receptors (Cedarbaum and Aghajanian 1977) and a high concentration of NE (Moore et al. 1979) is found in the locus coeruleus (LC), which plays an important role in the regulation of anxiety feelings in mammals and human. Neurosurgical removal of the LC in rats (Nassif et al. 1983) and in monkeys (Redmond et al. 1976; Huang et al. 1976) is followed by the disappearance of anxiety behaviour. Electrical stimulation of the LC in humans induces anxiety (Nashold et al. 1974). Neurons in this area are regulated mainly by autoinhibition (Andrade and Aghajanian 1984). Therefore a disproportionately high release of NE due to the reduced number of $\alpha_2$-receptor binding sites in the LC could lead to an enhancement of peripheral stimuli on their way to higher cortical and limbic areas, inducing anxiety. The pronounced expectation anxiety and the tendency of anxiety patients to overestimate their somatic response to stimuli (Rachman et al. 1988) would be in accordance with this therory.

The physiological importance of the regulatory properties of $\alpha_2$-receptors in anxiety is emphasised by the statistically significant positive correlations of receptor density and the affinity with the subjective ratings of anxiety and panicky feelings in the control group. With the increase in the level of NE due to anxiety/stress an increase in the number of presynaptic $\alpha_2$-receptors can be expected to autoregulate, i.e. reduce, the release of NE. The interdependency of the number of receptors and levels of catecholamines was shown in many in vitro (Toews et al.

1984) and in vivo experiments in humans (Brodde et al. 1984), mainly for β-adrenergic receptors. Whereas in normal controls this mechanism seemed to function regularly, patients with panic disorders seem not to be able to increase their number of $\alpha_2$-receptors, which leads to the overshooting release of NE.

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