Platelet Alpha-2-Adrenergic Dysfunction in Negative Symptom Schizophrenia: A Preliminary Study

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The specific binding to platelet membranes (B_{max}) of ^{3}H-clonidine, an alpha-2 agonist, and ^{3}H-yohimbine, an alpha-2 antagonist, was measured in nine drug-free male schizophrenic patients and repeated after 2 weeks of chlorpromazine (CPZ) treatment. Patients with a lower pretreatment B_{max} for ^{3}H-clonidine showed a significantly smaller change in B_{max} after treatment, less improvement in their clinical state, as indicated by the change in the Global Assessment Scale (GAS), and a lower posttreatment GAS. Also, they had a significantly higher score for negative symptoms on the Affect Rating Scale both before and after treatment. These findings suggest that schizophrenic patients with relatively subsensitive platelet alpha-2-adrenergic receptors, as measured by ^{3}H-clonidine binding, tend to have more negative symptoms and a diminished alpha receptor binding response and diminished clinical response to CPZ. There were no clinical correlations to ^{3}H-yohimbine binding.

Introduction

Recent studies of schizophrenia suggest abnormalities in the adrenergic nervous system (Hornykiewicz 1982; Sternberg et al. 1982; van Kammen and Antelman 1984). Some reports describe increased norephinephrine (NE) concentrations in postmortem limbic and striatal brain structures (Farley et al. 1978; Crow et al. 1979) and in cerebral spinal fluid (CSF) (Lake et al. 1980) of schizophrenic patients. Other studies reveal a variety of abnormalities of pre- and postsynaptic alpha-2 receptors in schizophrenic patients (Matussek et al. 1980; Ackenheil et al. 1982; Castellani et al. 1982; Sternberg et al. 1982).

Alpha-2-adrenergic receptors on human platelets are pharmacologically similar to the

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Received April 9, 1984; revised November 24, 1984.

0006-3223/85/$03.30

alpha-2 receptors in the brain (Garcia-Seville et al. 1981), and researchers have utilized the platelet alpha-2 receptor as a convenient model for what may be occurring in the brain. Kafka and van Kammen (1983), measuring the binding of tritiated dihydroergocryptine (^{3}H-DHE), an alpha-2 antagonist, found that the number of platelet alpha-2-adrenergic receptors is similar for schizophrenic patients and control subjects; however, there is an outlying group of schizophrenic patients whose platelets have a greater number of alpha-2 receptors than do platelets from controls or other schizophrenic patients.

Studies of mammalian brain reveal that alpha-2 receptors are blocked by neuroleptics, such as chlorpromazine (CPZ) (Peroutka et al. 1977). We have shown that a 2-week treatment with CPZ in previously drug-free schizophrenic patients reduces the number of platelet alpha-2 receptor sites (B_{max}), as shown by binding of ^{3}H-clonidine, an agonist, and ^{3}H-yohimbine, an antagonist (Rice et al. 1984). In examining the data from that study, we observed a bimodal distribution in the ΔB_{max} (difference between the ^{3}H-clonidine pretreatment B_{max} and the posttreatment B_{max}). Group I had a relatively high ΔB_{max} (>7), and Group II had a relatively low ΔB_{max} (<4).

Crow (1980) formulated the concept of Type I and II syndromes of schizophrenia. Type I is the "acute schizophrenic" with positive symptoms, and Type II syndrome is characterized by negative symptoms and a smaller response to neuroleptics. Andreasen and Olsen (1982) also described subtypes of schizophrenia by positive or negative symptoms.

The purpose of this study was to determine if the bimodal distribution of patients by the ΔB_{max} of ^{3}H-clonidine binding to platelets corresponds with any clinical characteristics.

Methods

The nine patients in the study were physically healthy schizophrenic males hospitalized at the Ann Arbor Veterans Administration Medical Center. Diagnosis was made through an interview by a senior attending psychiatrist according to Research Diagnostic Criteria for schizophrenia (Spitzer et al. 1977).

Patients were kept drug free for a period of at least 2 weeks prior to the study. The nature of the study and its procedures were explained to each patient, and a written informed consent was obtained.

All patients were administered the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960), the Global Assessment Scale (GAS), and the Affect Rating Scale (ARS) for affective flattening and affective overreactivity (Andreasen 1979). The time of administration of these scales coincided with pre- and posttreatment receptor binding studies.

All patients received CPZ for 14 days, with a dosage range of 200–800 mg/day (average dose, 458 mg/day). All patients who began the treatment with CPZ completed the 14-day drug treatment period. Eleven drug-free, physically healthy volunteers were matched for age, sex, and race and had no history of psychiatric illness.

Approximately 70 ml of blood was obtained by venipuncture between 8:00 and 9:00 AM from either schizophrenic patients or normal control subjects, and the specific binding of ^{3}H-clonidine and ^{3}H-yohimbine to platelet membranes was assessed as described previously (Garcia-Seville et al. 1981).

Student's two sample t-test and correlation of variables were used for statistical analysis. The level of significance was chosen as $p < 0.05$. Results are expressed as mean values plus or minus the standard deviation.

Results

The pretreatment B_{max} for ^{3}H-clonidine binding is directly related to posttreatment GAS ($p < 0.002$, $r = 0.8$), as well as to the change in GAS (ΔGAS) in response to treatment ($p < 0.03$, $r = 0.7$) (see Figure 1), and is inversely related to posttreatment ARS ($p < 0.04$, $r = 0.69$). In addition, the pretreatment B_{max} for ^{3}H-clonidine correlates significantly with the ΔB_{max} ($p < 0.0009$, $r = 0.90$) (see Figure 2). The dose of CPZ did not correlate with pretreatment B_{max} for ^{3}H-clonidine, ΔB_{max}, or any clinical scales.

The ΔB_{max} values for ^{3}H-clonidine binding divided the schizophrenics into two groups. Group I is defined as having a relatively larger ΔB_{max} (>7), whereas Group II had a relatively smaller ΔB_{max} (<4) in response to CPZ treatment. Group II had a significantly lower pretreatment B_{max} for ^{3}H-clonidine binding than did Group I ($p < 0.02$), whereas the difference between groups for pretreatment B_{max} for ^{3}H-yohimbine binding is not significant.

Group II had a significantly higher score for negative symptoms on the ARS, both pre- and posttreatment ($p < 0.02$), as well as lower pre- and posttreatment GAS scores ($p < 0.02$) when compared to Group I (Table 1). There were no significant differences between the two groups when comparing age of onset, duration of illness scores on HDRS, or dose of CPZ. The schizophrenic patients as a group had lower pretreatment B_{max} values for specific binding of ^{3}H-yohimbine to platelet membranes than did controls ($p < 0.025$), whereas the pretreatment B_{max} for ^{3}H-clonidine binding was not significantly different from controls. After 2 weeks of CPZ treatment, the B_{max} values for specific binding of both ^{3}H-clonidine and ^{3}H-yohimbine decreased significantly. These findings are discussed fully elsewhere (Rice et al. 1984).

Discussion

These findings suggest that the pretreatment B_{max} for ^{3}H-clonidine binding on platelets may help to predict response to CPZ treatment. The patients with a smaller pretreatment B_{max} had a smaller ΔB_{max} and had a poorer response to drug therapy, as measured by the change in GAS and posttreatment GAS. These patients also had more negative symptoms as measured by the ARS. The division of patients into distinct groups defined by ΔB_{max} may be interpreted as supporting the work of Crow (1980) and Andreasen and Olsen (1982), which describes a distinct group of patients with negative symptoms and poorer response to medications.

These data suggest that the group of schizophrenics who have negative symptoms may also have a subsensitivity of their platelet adrenergic receptors. Some studies have suggested subsensitive presynaptic alpha-adrenergic receptors in both the central nervous system (CNS) (Sternberg et al. 1982) and the peripheral nervous system (Castellani et al. 1982) of schizophrenic patients. However, these findings have not been correlated with clinical symptoms or treatment response. Increased ventricle to brain ratio (VBR) is associated with negative symptoms and decreased response to neuroleptics (Weinberger et al. 1979), and recently, van Kammen et al. (1983) demonstrated an association between increased VBR and low CSF dopamine β-hydroxylase activity, which suggests a possible loss of adrenergic neurons in those schizophrenic patients.

The difference between specific binding of the agonist, clonidine, and the antagonist, yohimbine, is thought to reflect the ability of clonidine to detect a subunit of the alpha2-

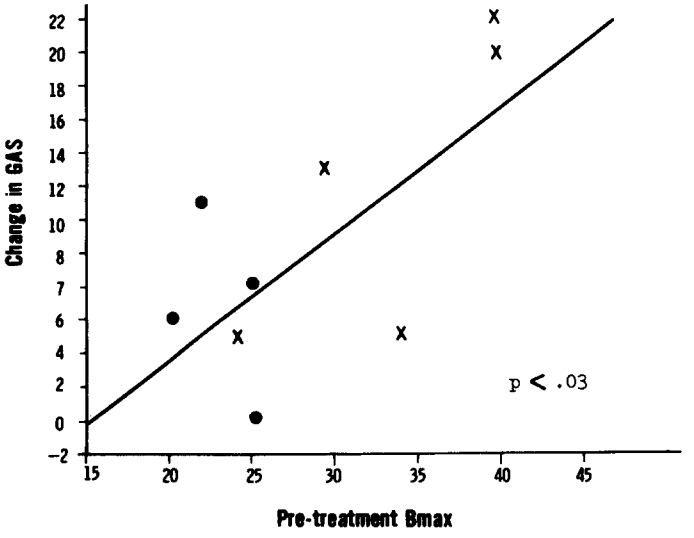

Figure 1. Relationship between pretreatment B_{max} for ^{3}H-clonidine binding and change in Global Assessment Scale following 2 weeks of CPZ treatment. ΔB_{max} is pretreatment B_{max} minus post-treatment B_{max}. (X) Group I ($\Delta B_{max} > 7$); (●) Group II ($\Delta B_{max} < 4$).

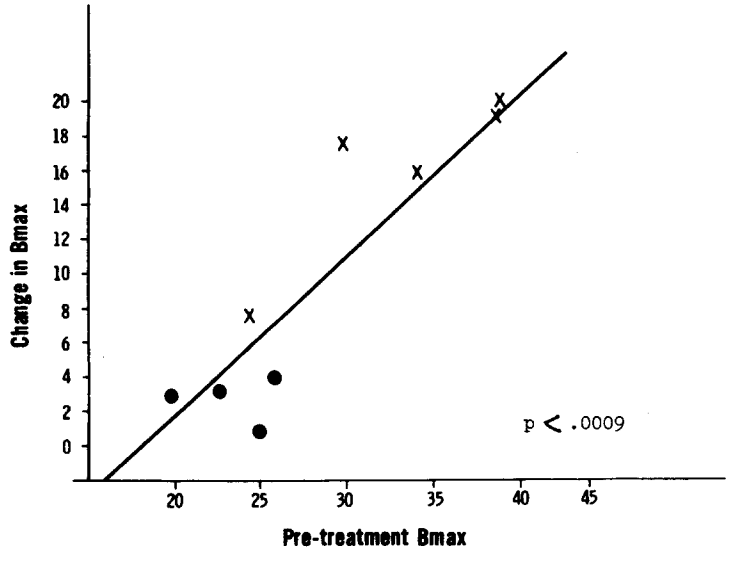

Figure 2. Relationship between pretreatment B_{max} for ^{3}H-clonidine binding and change in B_{max} following 2 weeks of CPZ treatment. ΔB_{max} is pretreatment B_{max} minus posttreatment B_{max}. (X) Group I ($\Delta B_{max} > 7$); (●) Group II ($\Delta B_{max} < 4$).

Table 1. Tritiated Clonidine, ARS, and GAS in Schizophrenics Before and After CPZ

Patient	Age	B_{max} for ^{3}H-clonidine binding[a] Before	After	Δ[b]	GAS Before	After	Δ[b]	ARS Before	After	Δ[b]
Group I[c]										
1	28	29.6	12.1	17.5	38	51	13	30	18	12
2	32	24.4	16.9	7.5	38	41	3	13	17	−4
3	38	34.1	18.5	15.6	38	42	4	21	17	4
4	27	38.1	19.8	19.0	33	55	22	16	15	1
5	34	39.0	18.9	20.1	40	60	20	15	9	6
Group II										
6	22	25.0	24.2	0.8	35	41	6	35	23	12
7	36	20.1	17.2	2.9	29	33	4	34	23	11
8	23	22.6	19.3	3.3	26	37	11	24	19	5
9	39	25.9	22.2	3.7	37	35	−2	32	30	2
Group I										
Mean	31.8	33.2	17.2	15.94	37.4	49.8	12.4	19.0	15.2	3.8
± SD	± 4.49	± 6.25[d]	± 3.06	± 5.01	± 2.61	± 8.23[d]	± 8.79	± 6.82[d]	± 3.63[d]	± 5.93
Group II										
Mean	30.0	23.4	20.7	2.7	31.6	36.5	4.8	31.3	23.8	7.5
± SD	± 8.76	± 2.60[e]	± 3.10	± 1.29	± 5.12	± 3.41	± 5.38	± 4.99	± 4.57	± 4.80
Controls (N = 11)	29.0 ± 1.9	35.0 ± 3.05								

[a] B_{max} is the maximum number of binding sites (fmol/mg protein) calculated by Scatchard analysis of full saturation curves for platelets from each subject.

[b] Δ, Pretreatment − posttreatment.

[c] Group I represents patients whose ΔB_{max} is > 7, Group II those patients whose ΔB_{max} is < 4.

[d] Significant mean difference between Group I and Group II, $p < 0.02$.

[e] Significant mean difference between Group II and controls, $p < 0.02$. There was no significant difference between Group I and controls.

adrenergic receptor (Garcia-Seville et al. 1981). It has been suggested that the affinity of the agonist for the binding site depends on the presence of guanosine-triphosphate (GTP) binding, whereas the antagonist binding is not dependent on this factor (Hoffman et al. 1982). Rotrosen et al. (1980) found reduced prostaglandin E_1 (PGE_1) stimulated adenylate cyclase activity in platelet lysates of some schizophrenics, and Kafka and van Kammen (1983) found that this reduced PGE_1 activity can be restored to normal levels with the addition of GTP. Steer and Wood (1979) have proposed two GTP binding sites on platelet membranes: one site interacts with PGE_1 binding, and the other site interacts with the alpha receptor. If the reduced PGE_1-stimulated adenylate cyclase activity in platelets is restored to normal by addition of GTP, and if adrenoreceptor agonist binding is also dependent on GTP, then the difference observed in this study between the B_{max} for ^{3}H-clonidine and the B_{max} for ^{3}H-yohimbine might indicate a defect in the regulatory unit involving the interaction of GTP with the platelet adrenergic receptor in schizophrenic patients with negative symptoms. Further studies are needed to test this hypothesis.

These results suggest that patients with lower pretreatment B_{max} for clonidine binding have a smaller ΔB_{max} in response to CPZ, which indicates a relatively subsensitive noradrenergic receptor system in platelets. These patients, defined as Group II, tend to

have more negative symptoms and a poorer response to medications when compared to other patients. Further studies in this area with a larger number of patients would help to clarify whether or not this relationship between diminished alpha-2-adrenergic receptor binding activity and negative symptoms is important clinically and pharmacologically and whether or not these differences in receptor binding exist in the CNS as well.

We thank Drs. Daniel P. van Kammen and Welmoet van Kammen for their assessments and suggestions in the preparation of this paper. We also thank David W. Smith, M.P.H., Ph.D., for his statistical assistance.

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