PLATELET SEROTONERGIC BINDING SITES IN MELANCHOLIC DEPRESSION WITH AND WITHOUT PSYCHOTIC FEATURES: RELATIONSHIP WITH CLINICAL AND FOLLOW-UP VARIABLES

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INTRODUCTION

Changes in the serotoninergic system have been widely reported in the aetiology of affective disorders and in suicidal behaviour (Owens and Nemeroff, 1994).
The 5-HT reuptake sites have been extensively studied in human blood platelets as well as in the brain using the radioligands [^{3}H]imipramine and [^{3}H]paroxetine (Rosel et al, 1997). Most of the studies have reported lower numbers of [^{3}H]imipramine binding sites in platelets from depressed patients, suggesting that this may be a biological marker of depression (Ellis and Salmond, 1994).

Studies using a more selective ligand for the 5-HT transporter, such as [^{3}H]paroxetine, have been more limited and have shown more controversial results.
Several studies have described higher numbers of 5-HT$_2$ receptors in blood platelets and in postmortem brains of depressed and suicidal patients. However, these results have not been confirmed by other reports.
Relationships between serotoninergic indices and clinical and lifetime course variables have not been extensively investigated in depression, and the results of the studies are inconclusive (Marazzitti and cols, 1988; Ellis and cols, 1990; Sheline and cols, 1995).

OBJECTIVE

The aims of the present study are:
- To determine if there are differences in platelet serotoninergic receptors between melancholic depressed patients with psychotic features, melancholic depressed patients without psychotic features, and a control group.
- To establish if there is any association between platelet serotoninergic markers and clinical and lifetime course variables in the patients group.

METHOD

Subjects
- Patients:
  - 42 consecutive hospitalized patients meeting DSM-IV criteria for unipolar major depression with melancholia, 20 with psychotic features and 22 without psychotic features.
  - 'Hamilton Depression Rating Scale' (HDRS, Hamilton, 1960) score ≥ 17.
  - Follow-up post discharge at the same hospital (mean ± SD: 77 ± 34 months).
  - *Exclusion criteria:* another axis I diagnosis, neurological or serious systemic diseases and previous treatment with lithium.
- Controls:
  - 40 healthy controls
  - *Exclusion criteria:* personal or familial psychiatric disorders, neurological or serious systemic diseases and previous treatment with lithium.

Written informed consent was obtained in all cases.

Clinical assessment

Patients
- **Systematic clinical data** were collected with the structured interview 'The Schedule for Affective Disorders and Schizophrenia' (SADS) (Endicott and Spitzer, 1978).
- **Symptom ratings at admission, at discharge and at follow-up** were assessed with the HDRS and 'Widlöcher Depression Retardation Scale' (Widlöcher, 1980).

Controls
- 'Goldberg Health Questionnaire' (Goldberg and Blackwell, 1970).
- 'Family History Research Diagnostic Criteria' (Andreasen and cols, 1977).

Biochemical assessment
- [^{3}H]Imipramine and [^{3}H]paroxetine binding sites and the 5-HT$_2$ receptor were simultaneously determined in blood platelet membranes of controls and patients after a pharmacological wash-out of 2 weeks.
- The 5-HT$_2$ receptor was labelled with the antagonist radioligand [^{3}H]ketanserin.

Statistical analysis
- The binding data were analyzed using the iterative nonlinear least squares curve fitting program EBDA, and values for maximum binding (B_{max}) and equilibrium dissociation constant (K_d) were determined from the Scatchard plots obtained. All curve fittings were performed on a specific binding.
- Differences between the three groups were analyzed using an analysis of variance, Scheffe procedure.
- Pearson's correlation coefficient was used to test associations when values were normally distributed; otherwise, the Spearman Correlation Coefficient was used. Association between biochemical parameters and follow-up variables were calculated with partial correlations, using the length of follow-up as the covariant.
- The level of significance was established as $p<0.05$.

RESULTS

Demographic and clinical data
Age and sex distribution for each group are shown in table 1. Symptom severity and course characteristics are shown in tables 2 and 3.

Table 1. Sample demographic characteristics

	Patients: Psychotic N = 20	Patients: Non-psychotic N = 22	Controls N = 40
	N (%)	**N (%)**	**N (%)**
Sex #			
Men	5 (25.0)	8 (36.4)	25 (62.5)
Women	15 (75.0)	14 (63.6)	15 (37.5)
	Mean ± SD	**Mean ± SD**	**Mean ± SD**
Years*	56.75 ± 9.11	61.00 ± 12.11	45.30 ± 14.11

SD: Standard deviation
#: Non-significant differences among the three groups (Chi-square).
**: Significant differences between the control group and both groups of patients (Oneway ANOVA, Scheffe test).*

Table 2. Symptom severity at baseline and at discharge

	Psychotic N = 20	Non-psychotic N = 22
	Mean ± SD	**Mean ± SD**
HDRS admission	28.30 ± 5.62	28.41 ± 7.85
HDRS discharge	3.32 ± 3.18	4.81 ± 4.07
ERDW admission	23.90 ± 11.92	23.95 ± 9.92
ERDW discharge	5.11 ± 4.26	4.81 ± 4.07

SD: Standard deviation
Non significant differences between psychotic and non psychotic patients (T-test)

Table 3. Course characteristics at baseline and follow-up (whole patients group)

	Mean ± SD
Age of onset (years)	49.41 ± 14.43
Duration of illness (months)	158.59 ± 119.86
Follow-up duration (months)	77.11 ± 33.91
Time to next episode (months)	53.21 ± 36.78

SD: Standard deviation

Biochemical results (table 4)
- [^{3}H]Imipramine B_{max} was decreased in both groups of melancholic patients compared with controls, without any differences between the psychotic and the non-psychotic subgroups (figure 1).
- Psychotic melancholic patients showed a significant decrease in 5-HT2 receptors Kd compared with the melancholic depressed patients without psychotic features and with the control group (figure 2).
- [^{3}H]Paroxetine binding did not differ between subgroups.

Clinical-biochemical correlations
- No significant correlations were found between any of the biochemical parameters and the severity of depression in both groups of patients.
- **Melancholic patients with psychotic features** showed an inverse correlation between 5HT2 receptors B_{max} and partial and complete recovery time ($r = -0.65$, $p = 0.002$ and $r = -0.56$, $p = 0.01$, respectively). Furthermore, patients with suicidal ideation/attempts show a decrease in [^{3}H]-imipramine K_d (0.95 ± 0.05 vs 1.26 ± 0.32, $p = 0.048$) and [^{3}H]paroxetin K_d (0.05 ± 0.01 vs 0.07 ± 0.31, $p = 0.012$).
- **Melancholic patients without psychotic features** showed a significant inverse correlation between [^{3}H]paroxetin B_{max} and the time to recurrence after recovery from the index episode ($r = -0.43$, $p = 0.047$).

Table 4. Binding parameters in melancholic patients with and without psychotic features and controls

	Patients: Psychotic N = 20	Patients: Non-psychotic N = 22	Controls N = 40
	Mean ± SD	**Mean ± SD**	**Mean ± SD**
3H-imipramine			
B_{max}*	1148.70 ± 644.97	1179.18 ± 483.11	1866.27 ± 493.04
K_d#	1.09 ± 0.34	1.20 ± 0.39	1.18 ± 0.46
3H-paroxetina			
B_{max}#	1486.65 ± 401.43	1352.45 ± 387.71	1426.70 ± 467.63
K_d#	0.06 ± 0.01	0.05 ± 0.01	0.06 ± 0.01
5-HT2			
B_{max}#	132.80 ± 75.90	145.77 ± 61.91	130.40 ± 73.61
K_d**	0.91 ± 0.24	1.03 ± 0.40	1.18 ± 0.46

SD: Standard deviation
"Bmax (fmol/mg proteina); Kd (nM/l)."
**: Significant differences between control group and both groups of depressed patients (Oneway ANOVA, Scheffe test).*
*** : Significant diferentes between psychotic depressed patients and control group (Oneway ANOVA, Scheffe test).*
#: Non-significant differences between groups (Oneway ANOVA).

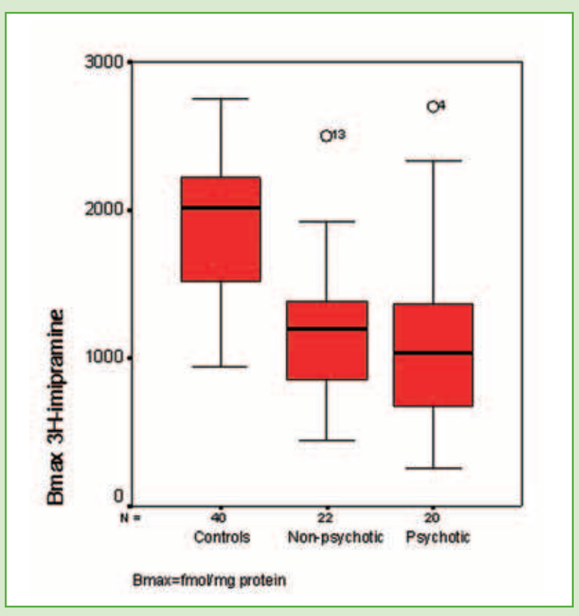

Figure 1. 3H-Imipramine Bmax distribution

CONCLUSIONS

- This study provides support for the hypothesis that the maximum binding of [^{3}H]imipramine, but not [^{3}H]-paroxetine platelet 5-HT uptake sites are reduced in melancholic depression with and without psychotic symptoms.
- Evidence suggests that 5-HT2 binding affinity may allow differentiation between melancholic depressed patients with and without psychotic features.
- The presence/absence of psychotic features may be taken into account in the study of the relationship between platelet serotoninergic markers and clinical and lifetime course variables in melancholic depression.

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