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INCREASE IN RED BLOOD CELL TRIIODOTHYRONINE UPTAKE IN UNTREATED UNIPOLAR MAJOR DEPRESSED PATIENTS COMPARED TO HEALTHY VOLUNTEERS

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Abstract

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1. Kinetic parameters of red blood cell (RBC) L-triiodothyronine (T3) initial uptake (Vmax, maximal velocity and Km, Michaelis constant) were determined in 34 untreated inpatients suffering from unipolar depression and in 40 healthy volunteers.
2. Both Vmax and Km were significantly increased in depressed patients as compared to controls. The alterations in kinetic parameters were not associated with the severity of depression.
3. Out of the 19 depressed patients who were submitted to TRH test, 7 of them (36%) showed a blunted TRH-induced TSH response associated with a Vmax situated outside the control mean value ± 1 S.D.
4. The authors found a significant positive correlation between Vmax of RBC L-T3 and L-tryptophan (TRP) uptakes which is in agreement with the assumption that L-T3 and L-TRP share a common carrier system at the erythrocyte level.
5. The results indicate that the uptake of L-T3 by RBC is increased in major depression. These transport perturbations might reflect alterations in the plasmatic metabolism of L-T3. Evaluation of RBC L-T3 uptake could be useful in a best biological characterization of the depressed patients with regard to their thyroid function.

Keywords: erythrocyte, L-triiodothyronine, L-tryptophan, major depression, transport, TRH test.

Abbreviations: free triiodothyronine (FT3), free thyroxine (FT4), Hamilton Rating Scale for Depression (HRSD), initial velocity (Vi), L-triiodothyronine (L-T3), L-tryptophan (L-TRP),

maximal velocity (Vmax), Michaelis constant (Km), red blood cells (RBC), thyrotropin (TSH), thyrotropin-releasing-hormone (TRH), tricyclic antidepressants (TCA).

Introduction

There is a large body of literature evidencing a strong relationship between mood disorders and disturbances of the thyroid axis (Joffe and Levitt, 1993). However, the biological substratum of this association remains to be clarified.

Since the last century, many studies have shown that mood disorders are present in patients who have clinical evidence of thyroid diseases. About 40% of the patients suffering from primary hypothyroidism have depressive disorders and hypothyroidism is more frequently observed in the depressed population (8% to 15%) than in the general one (0.2% to 0.5%) (Kirkegaard et al., 1990). Although the vast majority of patients with primary affective illness have thyroid function explorations within the normal range (Loosen, 1986; Bauer and Whybrow, 1988), some studies have shown alterations in baseline serum thyroid hormone levels in depressed patients. Serum total or free L-triiodothyronine (T3) levels have been found to be decreased (Kirkegaard et al., 1975; Joffe et al., 1985; Orsurlak et al., 1985) or normal (Kirkegaard, 1981; Roy-Byrne et al., 1984; Unden et al., 1986) in the depressed patients. A subclinical hyperthyroidism, revealed by a blunted thyrotropin (TSH) response to thyrotropin-releasing hormone (TRH) administration (the TRH test) associated with normal plasma T3 and thyroxine (T4) levels, is a frequent starting factor for mood disorders in predisposed subjects (Extein et al., 1984). Approximately 30% of depressed patients show a blunted TRH test (Loosen, 1992), but this test appears to have no value in the diagnosis of depression (Vaughan et al., 1991; Joffe and Levitt, 1993) and to have no specificity in depressive illness (Loosen, 1992).

The relationship between thyroid axis and depression is also illustrated by the efficacy of thyroid hormones in the treatment of affective disorders (Joffe et al., 1995). L-T3 has been shown to potentiate the response to tricyclic antidepressants (TCA) (Wilson et al., 1970) and to convert TCA non-responders in responders to treatment (Prange et al., 1969; Coppen et al., 1972; Goodwin et al., 1982; Schwarcz et al., 1984; Joffe et al., 1993).

Nevertheless, there is no clinical or biological predictive indicator of the clinical effectiveness of thyroid hormones in depressive disorders.

Red blood cells (RBC) possess a membrane carrier-mediated system specific for L-T3. This transport system is saturable, stereospecific, energy and Na^+-independent (Holm and Jacquemin, 1979; Docter et al., 1982; Osty et al., 1990). L-T3 enters the cell by facilitated diffusion and is accumulated but not metabolized in the cell. RBC play likely a role in interorgan transport of L-T3 and act as a circulating pool of the hormone (Osty et al., 1988; 1990). Recently, it has been shown that L-T3 shares the erythrocyte transport system for L-tryptophan (TRP), the T system (Zhou et al., 1990; Samson et al., 1992; Zhou et al., 1992). The authors have recently reported the existence of perturbations in the kinetic parameters of RBC L-TRP uptake in untreated depressed patients (Jeanningros et al., 1996). The patients could be divided into three subgroups with high, normal and low Vmax. As the circulating blood cells play likely a role in L-TRP homeostasis, we have suggested that these abnormalities in RBC L-TRP uptake reflect a disturbance in dynamic regulation of L-TRP plasma availability on which cerebral serotonin synthesis closely depends (Fernstrom and Wurtman, 1972; Wurtman et al., 1981; Leathwood, 1987; Young and Teff, 1989).

The aim of the study was to examine the kinetic parameters (Vmax and Km) of RBC L-T3 initial uptake in unmedicated inpatients suffering from major unipolar depressive disorders and to analyze them in relation to their thyroid status. In addition, the kinetics of L-TRP and L-T3 uptakes were determined in parallel in some of the patients.

Methods

Controls

The control group consisted of 40 healthy subjects. They were enrolled from the laboratory staff, medical students and their acquaintances after giving their informed consent (18 men and 22 women, mean age ± S.D. = 33.1 ± 11.3 years, range 21-67), with no history of thyroid or psychiatric illness. None of the controls were employed in the laboratory of the authors.

Patients and Clinical Procedures:

Thirty four hospitalized depressed patients (13 men and 21 women, mean age ± S.D. = 46.6 ± 12.8 years, range 19-72) participated in the study after giving their informed consent. The study was approved by the ethics committee of the Medical Faculty of the University of Aix-Marseille II. Patients were classified according to the DSM-III-R criteria (Diagnostic and Statistical Manual of Mental Disorders, 3rd Ed. revised, American Psychiatric Association, 1987). Diagnoses were made on the basis of the Structured Clinical Interview for DSM-III-R Patient Version (Spitzer et al., 1985). All patients met the criteria for major unipolar depressive disorder (10 with melancholic characters). At the time of the sampling, the severity of depression was assessed using the Hamilton Rating Scale for Depression (HRSD, 26 items, Hamilton, 1967). The mean HRSD score ± S.D. was 30.7 ± 7.2. The patients remained free of antidepressant medications for at least 7 days prior to testing. Thirteen patients had never received antidepressants before the hospitalization (drug-naive). Among the 21 patients who had received antidepressants before the 7 day wash-out period (drug-withdraw), none were on antidepressants with long-lived metabolites. During the wash-out period, 31 patients received small doses of benzodiazepines for sleep induction (equivalent to 10 mg of diazepam). Patients with other psychiatric disorders, drug or alcohol addiction, or with organic and endocrine diseases, included thyroid disease, were excluded from the study.

Chemicals:

[3'-^{125}I]-triiodo-L-thyronine (specific activity: 1200 μCi/μg) was purchased from Johnson and Johnson Clinical Diagnostics (Les Ulis, France), L-[^{3}H] tryptophan (specific activity 25-31 Ci/mmol) from Dupont de Nemours (N.E.N., Paris, France). 3, 3', 5-triiodo-L-thyronine and L-tryptophan was purchased from Sigma (Paris). Plastic tubes and pipette tips were silicone-treated with Sigmacote (Sigma).

L-T3 Uptake Determination:

Both patients and controls were sampled after an overnight fast between 8:00 am and 9:00 am. Ten milliliters of blood were withdrawn by venipuncture on glass tubes containing lithium heparinate as anticoagulant and were treated within the following two

hours. The protocol used was previously described by Osty et al. (1990). The plasma and the buffy coat were removed and the erythrocyte pellet was washed twice with cold buffer A (NaCl = 137 mM; KCl = 2.7 mM; Na_2HPO_4 = 8.1 mM; KH_2PO_4 = 1.5 mM; pH 7.5), then centrifuged (2200 g, 10 min, 4°C) and once more in cold buffer B (NaCl = 125 mM; KCl = 20 mM; $MgCl_2$ = 4 mM; D-Glucose = 10 mM; Na_2HPO_4 = 4.05 mM; NaH_2PO_4 = 0.95 mM; pH 7.4). Then, the erythrocyte pellet was suspended in the cold buffer B. The cell concentration was determined in an automatic cell counter. Washed erythrocytes were kept on ice in order to stabilize their metabolic state prior to incubation. RBC were prewarmed for 15 min at 37°C. The reaction was initiated by mixing erythrocytes (10^8 cells/ml) in buffer B at 37°C with [^{125}-I] L-T3 as tracer ($\approx 10^5$ cpm/ml) and unlabeled L-T3 (7 concentrations ranging from 5 nM to 200 nM plus one concentration at 10 μM for the determination of unsaturable uptake). Reaction was pursued for 2 min in order to satisfy the initial rate conditions. The incubation was stopped by adding 2 ml of the cold buffer B containing unlabeled L-T3 (3.10^{-5}M) and cooling in an ice bath. At this concentration, the extracellular L-T3 inhibits the efflux of intracellular L-T3 by a trans-inhibition mechanism described by Osty et al., (1988). The RBC were collected by centrifugation (2000g, 3 min, 4°C) and washed twice with ice-cold buffer A, containing 10^{-5} M unlabeled L-T3, in order to eliminate the L-T3 which was not incorporated. Then, the radioactivity associated with the erythrocyte pellet was measured in a gamma counter. The uptake assays were performed in triplicate.

The initial velocity (Vi) of L-T3 total uptake was measured and saturable uptake was calculated by subtracting the unsaturable uptake. The ratio Vi/S was calculated, S being the concentration of L-T3 in the incubation medium, and was used to construct Eadie-Hofstee plots of the data (Fig 1). The Km (slope) and Vmax (y-intercept) values were obtained by linear regression.

L-Tryptophan Uptake Determination:

The authors examined RBC L-TRP uptake in parallel with L-T3 uptake in 19 of the 34 depressed patients. The kinetic parameters of L-TRP uptake were determined in washed RBC using L-[^{3}H] TRP as described previously by Jeanningros et al. (1996). Briefly, blood samples (10 ml) anticoagulated with EDTA were centrifuged at 4800g for 10 min at room temperature. Plasma and platelet were removed and the RBC pellet was washed

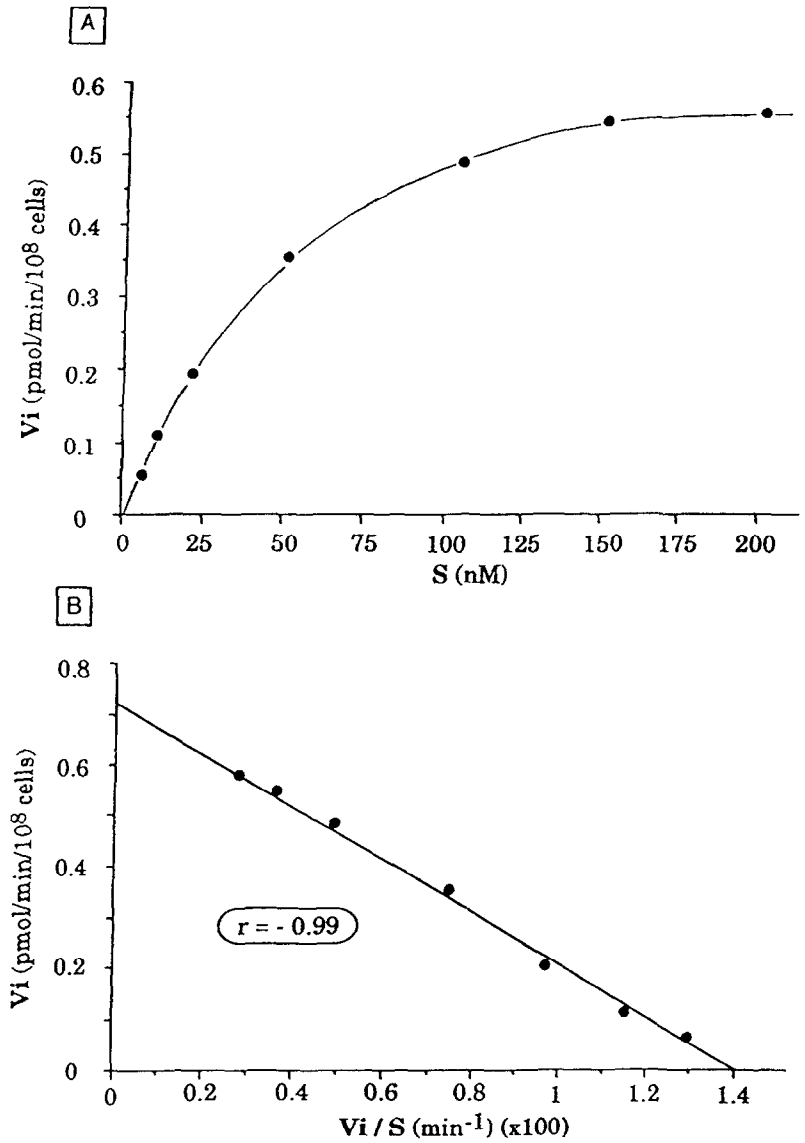

Fig 1: A/ Initial velocity (Vi) of the L-T3 uptake by erythrocytes after 2 min incubation at 37°C versus unlabeled L-T3 concentration in medium (S).
B/ Eadie-Hofstee plots of L-T3 uptake by RBC from a control subject. Km (slope) and Vmax (y-intercept) values were obtained by linear regression.

three time at 37°C in order to eliminate the intracellular TRP content by adding 4 volumes of buffer (NaCl = 137.98 mM; KCl = 4.69 mM; $MgSO_4$-$7H_2O$ = 1.18 mM; KH_2PO_4 = 1.17 mM; TRIS = 14.4 mM; pH 7.3). Uptake was initiated by adding 300 µl of TRP (10 concentrations ranging from 0.1 mM to 5 mM prepared with [^{3}H]-TRP as tracer) to 100 µl of RBC pellet. The reaction was pursued at 37°C for 1 min and then stopped by adding cold buffer and centrifuging 4 min at 8000g at 4°C. After removing the supernatant and rinsing tubes, RBC were lysed with perchloric acid (30%). After centrifugation, each supernatant was collected in triplicate and counted in liquidscintillation.

Thyroid Function Evaluation:

Serum concentrations of free T3 (FT3), free T4 (FT4) and basal TSH were measured at the same time of the samplings. FT3 and FT4 assays were carried out by immunoluminometric assays (Amerlite®-MAB FT3 and FT4, Johnson & Johnson Clinical Diagnostics, Les Ulis, France). The euthyroid range was 3.8-8.0 pM for FT3 values and 7.0-25.0 pM for FT4 values. TSH assays were carried out by immunoluminometric assay (LUMItest® hTSH, Hoechst-Behring, Rueil-Malmaison, France). The euthyroid range for basal TSH was 0.3-4.0 mU/l. Nineteen patients were submitted to TRH test, i.e. measurement of serum TSH 10, 20 and 30 min following TRH administration (StimuTSH®, 200 µg). Patients with a Δ TSH lower than 7 mU/l, i.e. difference between the higher and basal level of TSH, were considered showing a blunted TRH test.

Statistical Analysis:

Comparisons of kinetic parameters between depressed patients and controls, or males and females were performed by the Mann-Whitney U test. Correlational analyses between 2 quantitative parameters were made with Spearman order correlation coefficient.

Results

Demographic and clinical data of patients and controls are outlined in Table 1.

Table 1

Demographic and Clinical Variables

	Control Subjects	Depressed Patients
Number	40	34
Age (years)	33.1 ± 11.3	46.6 ± 12.8 *
Males : Females	18 : 22	13 : 21
HRSD score	——	30.7 ± 7.2

Age and HRSD score are expressed as mean ± S.D.
Significantly different from controls: * $p < 0.0001$, Mann-Whitney U test.

L-T3 Uptake:

The intra-assay variation coefficients for the determination of Vmax and Km were 10.9% and 14.4% respectively. In the control group, the mean Vmax value ± S.D. of the L-T3 uptake was 0.80 ± 0.16 pmol/min/10^8 cells and the mean Km value ± S.D. was 59.9 ± 10.3 nM (Table 2). No correlation was observed between age and any of the kinetic parameters.

In depressed patients, both the kinetic parameters were significantly increased as compared to the controls (mean Vmax ± S.D. in pmol/min/10^8 cells = 0.97 ± 0.30 and 0.80 ± 0.16 respectively, $p < 0.01$ and mean Km ± S.D. in nM = 71.4 ± 22.1 and 59.9 ± 10.3 respectively, $p < 0.02$) (Table 2). However, there was an overlap in kinetic parameters between patients and controls (Fig 2). Indeed, 11 (32%) depressed patients had Vmax values outside 2 S.D. from the control mean: 9 (26%) above 2 S.D. (16 above 1 S.D.) and 2 (6%) below 2 S.D. (5 below 1 S.D.).

There was no difference in the distribution of males and females between controls and depressed patients (Chi 2 = 0.21; $p = 0.6$, NS) (Table 1). No significant difference was observed between males and females either in Vmax (mean ± S.D. in pmol/min/10^8 cells = 0.89 ± 0.35 and 1.01 ± 0.27 respectively, NS) or in Km (mean ± S.D. in nM = 72.4 ± 24.7 and 70.8 ± 21.0 respectively, NS) (Table 2). There was a significant negative correlation between Vmax values and the age of the depressed patients ($r = -0.4$, $p < 0.01$) but not between Km values and age ($r = -0.1$, NS). When patients and controls were matched for

age (n=19), Vmax and Km were still significantly higher in patients than in controls (mean Vmax ± S.D. in pmol/min/10^8 cells = 1.03 ± 0.31 and 0.83 ± 0.15 respectively, p= 0.01 and mean Km ± S.D. in nM = 72.8 ± 17.8 and 59.4 ± 9.2 respectively, p< 0.01).

Table 2

Kinetic Parameters of L-T3 Uptake in Controls and Unipolar Major Depressed Patients

	Number	Vmax (pmol/min/10^8 cells)	Km (nM)
Controls	40	0.80 ± 0.16	59.9 ± 10.3
Depressed patients	34	0.97 ± 0.30 **	71.4 ± 22.1 *
men	13	0.89 ± 0.35	72.4 ± 24.7
women	21	1.01 ± 0.27	70.8 ± 21.0
Patients without melancholia	24	0.97 ± 0.35	70.3 ± 24.1
Patients with melancholia	10	0.95 ± 0.13	74.0 ± 17.9
Patients with normal TRH test	12	0.94 ± 0.24	77.0 ± 29.6
Patients with blunted TRH test	7	0.98 ± 0.40	68.1 ± 22.5

Values are expressed as means ± S.D.
Significantly different from controls: ** p< 0.01, * p< 0.02, Mann-Whitney U test.

There was no significant correlation between the values of the kinetic parameters and the HRSD scores. There was no significant difference either in Vmax or in Km between depressed patients with and without melancholia (mean Vmax ± S.D. in pmol/min/10^8 cells = 0.95 ± 0.13 (n= 10) and 0.97 ± 0.35 (n= 24) respectively, NS and mean Km ± S.D. in nM = 74.0 ± 17.9 and 70.3 ± 24.1 respectively, NS) (Table 2). There was no significant difference either in Vmax or Km between patients who had and those who had not received benzodiazepines during the wash-out period (mean Vmax ± S.D. in pmol/min/10^8 cells = 0.98 ± 0.31 (n= 31) and 0.83 ± 0.23 (n=3) respectively, NS and mean Km ± S.D. in nM = 71.6 ± 23.3 and 68.9 ± 10.0 respectively, NS). The authors did not observe any difference

in kinetic parameters between drug-naive and drug-withdraw patients (mean Vmax ± S.D. in pmol/min/10^8 cells = 0.91 ± 0.31 (n= 13) and 1.00 ± 0.30 (n= 21) respectively, NS and mean Km ± S.D. in nM = 63.5 ± 15.8 and 76.2 ± 24.8 respectively, NS).

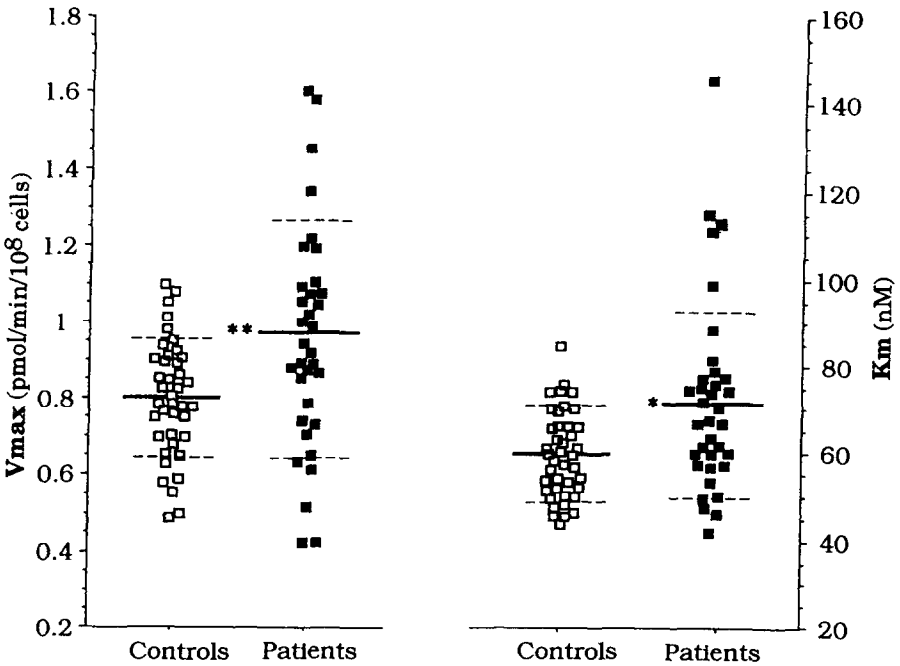

Fig 2: Scattergram of the kinetic parameters of L-T3 uptake in RBC from control subjects (n= 40) and unipolar major depressed patients (n= 34).
Significantly different from controls, Mann-Whitney U test:** ($p< 0.01$), * ($p< 0.02$)
——— Mean value ; -------- ± 1 S.D.

L-TRP Uptake:

In the 19 patients in which both L-T3 and L-TRP uptakes were determined in parallel, the Vmax of L-T3 uptake was significantly different from control value (mean Vmax ± S.D. in pmol/min/10^8 cells = 0.94 ± 0.23 and 0.80 ± 0.16 respectively, $p< 0.01$). The Vmax values of the two transports were significantly positively correlated ($r= 0.54$, $p< 0.02$) (Fig 3).

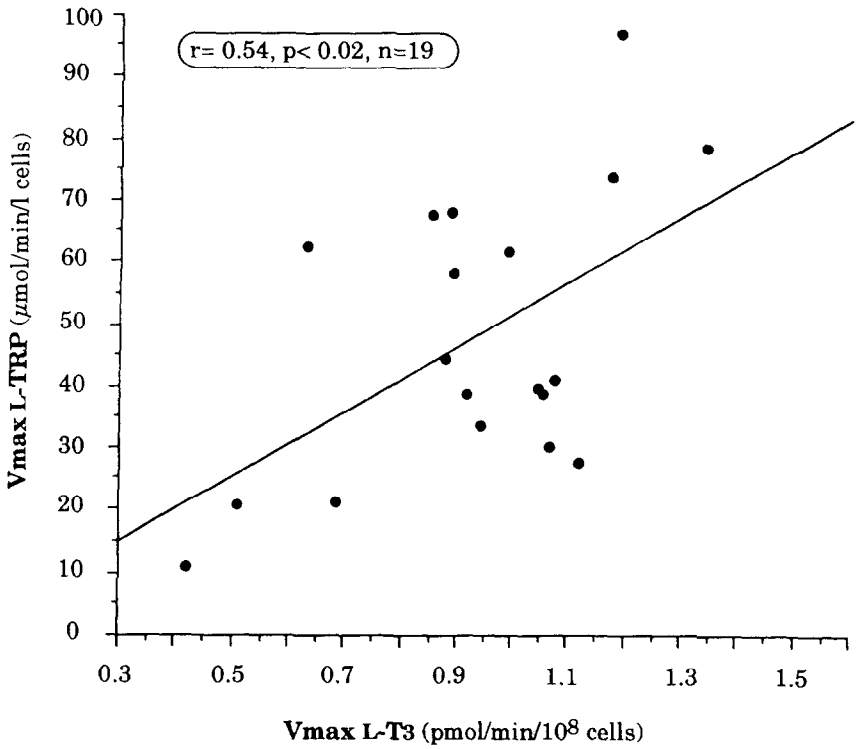

Fig 3: Significant positive correlation between Vmax of L-TRP and of L-T3 uptakes by RBC in unipolar major depressed patients.

Thyroid Function Evaluation:

All patients showed normal serum FT3, FT4 and basal TSH levels (mean ± S.D. = 5.05 ± 0.94 pM; 13.9 ± 3.12 pM; 1.72 ± 1.25 mU/l, respectively). Seven (36%) of the 19 depressed patients who were submitted to a TRH test showed a blunted TSH response (Table 2). There was no significant difference in kinetic parameters between patients with normal and blunted TSH response to TRH (mean Vmax ± S.D. in pmol/min/10^8 cells = 0.94 ± 0.24 and 0.98 ± 0.40 respectively, NS and mean Km ± S.D. in nM = 77.0 ± 29.6 and 68.1 ± 22.5 respectively, NS). However, all the patients with a blunted TRH test had Vmax values

outside 1 S.D. from the control mean: 4 had a Vmax exceeding 1 S.D. and 3 had a Vmax inferior to 1 S.D. from the control mean.

Discussion

Alterations in RBC L-T3 Uptake in Depressed Patients

The results provide the first evidence of an increase in the kinetic parameters of the L-T3 membrane-carrier-system in RBC of untreated patients suffering from major unipolar depressive disorder. The modification in transport kinetics does not appear to be due to any difference in the demographic characteristics of the experimental groups. The authors found no effect of sex on the kinetic parameters. Although they observed a negative correlation between Vmax values and age in the depressed group, the increase of Vmax in patients cannot be related to their age since the patients were older than controls. They do not think that the low doses of benzodiazepines received by some of the patients during the wash-out period had affected the RBC L-T3 uptake since they found no difference in kinetic parameters between patients who had and those who had not received benzodiazepines.

Vmax and Km values were more scattered in depressed patients than in controls. There was a substantial overlap of the kinetic parameters between the two groups, which indicates a biological heterogeneity of the depressed patients with regard to this transport system. The severity or the melancholic subtype of the depression do not account for the differences in individual Vmax and Km values of L-T3 uptake observed in the patients.

Pathophysiological Significance:

Erythrocytes take up L-T3 by means of a carrier-mediated system which is saturable, equilibrative and Na^+-independent (Holm and Jacquemin, 1979; Docter et al., 1982; Osty et al., 1990). Since the Km of L-T3 uptake is three orders of magnitude higher than the plasma FT3 level, this transport system is not saturated under physiological conditions. As it has been reported by Osty et al. (1988), the concentration of RBC-associated L-T3 might be more than 10-fold higher than the FT3 plasma concentration. RBC do not metabolize the hormone. They play likely a role in the blood transport and peripheral

homeostasis of L-T3 as this circulating pool is easily and rapidly exchangeable with target tissues (Francon et al., 1990; Osty et al., 1990). It can be expected that the increase in kinetics of L-T3 uptake observed in depressed patients have repercussions on the dynamics of the blood supply of the hormone.

Assessment of plasma thyroid hormone levels in depression have produced inconsistent findings. The vast majority of reports indicate that patients with affective illness have thyroid hormone levels within the euthyroid range (Joffe and Levitt, 1993; Joffe and Sokolov, 1994). In the present study, the basal levels of plasma FT3 of the depressed patients are in a normal range. It is nevertheless possible that the modifications of L-T3 carrier system reflect a not yet known perturbation at the systemic level. The authors have recently evidenced changes in kinetic parameters of RBC L-T3 uptake in rats in response to changes in plasma levels of thyroid hormones : Vmax was increased in hypothyroid rats and it was decreased in hyperthyroid rats (manuscript in preparation). Furthermore, Picò et al. (1992) reported that RBC uptake of amino-acids was durably modified following chronic abnormal metabolic conditions, such as obesity. In the same way, perturbations in L-T3 uptake could be induced by chronic metabolic disturbances which cannot be revealed by usual determinations of basal levels of thyroid hormones in serum.

Relationship with L-TRP Uptake:

According to Samson et al. (1992) and Zhou et al. (1992), the carrier-mediated system used by L-T3 to enter the RBC seems to be the T system which has been first described as specific for L-TRP (Rosenberg et al., 1980; Rosenberg, 1981). At this level, the two substrates are subject to a functional interaction, in particular a competitive inhibition for the entry into the cell (Zhou et al., 1990). So, perturbations in L-T3 uptake likely result in perturbations in L-TRP uptake and in turn in the plasma L-TRP availability on which 5-HT synthesis in the brain crucially depends. The authors have recently described alterations in RBC L-TRP uptake in untreated depressed patients (Jeanningros et al., 1996). The authors found a significant positive correlation in Vmax values between RBC L-TRP and L-T3 uptakes in the depressed patients. This result is in line with the previous reports of a functional interaction between these two substrates for the T system (Samson et al., 1992; Zhou et al., 1992).

Relationship with TRH Test:

The TRH test has been widely used for the thyroid exploration of affective disorders. It has been found to be blunted in approximately one third of the depressed patients (Loosen and Prange, 1982; Nemeroff and Evans, 1989; Loosen, 1992). A blunted TRH test, with normal T3, T4 and basal TSH, can reflect a subclinical hyperthyroidism (Joffe and Levitt, 1993). For Musselman and Nemeroff (1996), in depression, the blunted TRH test is rather due to a chronic hypersecretion of TRH in the median eminence. The data in the present study confirm that about one third of patients shows a blunted TSH response to TRH. Although there is no clear evidence of a relationship between blunted TRH test and modifications in RBC L-T3 uptake, the patients with blunted TRH test tend to present rather high or low Vmax values.

Accumulated clinical data evidence the effectiveness of T3 in association with antidepressants in some resistant depressions (Joffe et al., 1995). Now, there is no biological or clinical predictive indicator for the success of a L-T3 adjunctive therapy. The TRH test in combination with the RBC L-T3 uptake might be useful to identify a subgroup of depressed patients that could benefit from a such therapeutic association. But further investigations are required to bear out this assumption.

Conclusion

The data show an increase in kinetic parameters of RBC L-T3 uptake in major unipolar depressed patients. Although, the exact pathophysiological significance of the alteration remains to be elucidated, the results shed a new light on the interactions between thyroid axis and depression.

Acknowledgments

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