TRYPTOPHAN AND SEROTONIN IN BLOOD AND PLATELETS OF DEPRESSED PATIENTS: EFFECT OF AN ANTIDEPRESSANT TREATMENT

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SUMMARY

Platelets have serotonin (5-HT) uptake and storage mechanisms similar to those from neurons. In addition, they represent nearly 99% of blood 5-HT concentration. For these characteristics, platelets are considered useful biomarkers of the serotonergic synaptic neurotransmission, particularly in psychiatric disturbances such as depression. However, most studies which have evaluated platelet 5-HT concentrations in depression have not shown similar findings.

It has been suggested that changes in plasma tryptophan (TRP) concentrations might modify 5-HT concentration in the brain, as well as in platelets. Likewise, decreased plasma concentrations of TRP have been found in depressed patients, and the selective 5-HT reuptake inhibitors (SSRIs) induce changes in platelet 5-HT concentration.

Considering the controversy surrounding platelet 5-HT concentrations in depressed patients, and the fact that blood 5-HT and TRP have not been studied in the Mexican population, we decided to study 5-HT and tryptophan concentrations in blood and platelets from depressed and control Mexican subjects to evaluate a possible correlation with the severity of depression. The effect of fluoxetine and citalopram treatment on blood and platelet 5-HT and TRP concentrations in depressed patients was also studied.

Material and methods

Depressed patients

The patients of this study were carefully selected and evaluated. Scales based on semi-structured interviews were applied (MINI and SCID-II) by clinical investigators to reduce any possible bias in patient selection. The influence of the seasonal variability on the 5-HT or TRP blood concentrations was controlled by pairing depressed patients and healthy subjects according to age, gender and, in the case of women, menstrual cycle phase. Patients with a complete remission of depression symptoms (defined as a score not higher than 5 points in the Hamilton's scale, and lower than 7 points in Beck's scale) were asked for a blood sample to measure platelet and blood concentrations of 5-HT and TRP. The patients were weighted before the treatment and after their improvement.

Control subjects

The control group was integrated by 30 healthy subjects, 24 women and 6 men, with an average age of 32.3 ± 10.8 years. Participants were recruited from the overall Mexican population, interviewed by a psychiatrist, and evaluated with the structured interview MINI and the SCID-II, all these to discard any psychiatric diagnose. None of them had received any pharmacological treatment during the three weeks prior to the study. Control and depressed women were paired according to their menstrual cycle phase.

All participants received a detailed explanation of the study, and those who voluntarily accepted the stipulations signed an informed consent document. Control and patient subjects were clinically examined and studied with routine laboratory tests (blood count, blood chemistry, urinalysis, and thyroid function test).

Blood sample procedures

5-HT and TRP measurements in total blood preparation were carried out according to the method described by Anderson, and were quantified by high performance liquid chromatography (HPLC).

Statistical analysis

The differences were statistically determined through an analysis of variance (ANOVA), with the assistance of the SPSS 12.00 (Statistical Software by SPPS Inc.).

Results

Results from laboratory tests, such as blood count, blood chemistry, thyroid function (T3, T4 and TSH) and urinalysis were normal in depressed subjects, as well as in healthy volunteers.

Platelet number, blood 5-HT concentration, platelet content of 5-HT, and blood tryptophan concentration showed no significant differences in depressed patients in comparison to control subjects. 5-HT values in blood and platelet were significantly lower than the initial concentrations in patients after antidepressant treatment.

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Discussion and conclusions

Discrepancies between our study and those found in the literature can be explained with three different approaches: ethnical, physiological, and methodological, as is further discussed.

The significant decrease produced by the antidepressant treatment in blood and platelet serotonin concentration may be a consequence of the action of SSRIs, due to a 5-HT diminished uptake by the platelet.

Considering our results, we conclude that:

1. Blood and platelet 5-HT concentrations were not different between depressed patients and healthy volunteers.
2. Blood TRP concentrations were not different between depressed patients and healthy volunteers.
3. SSRIs (fluoxetine or citalopram) used in the treatment of depressed patients induced a significant decrease in blood and platelet content of 5-HT, and had no effect in TRP concentrations.
4. Based on these results, neither blood/platelet 5-HT nor blood tryptophan concentrations seem to be good biological markers of depressive patients status. However, 5-HT, but not tryptophan, might be a reference point for pharmacological treatment effect.

Key words: Depression, 5-Hydroxitryptamine, platelet, tryptophan, antidepressants.

RESUMEN

Debido a que las plaquetas tienen un mecanismo de recaptura y almacenamiento de serotonina y acumulan alrededor de 99% del total de la serotonina en sangre, la serotonina plaquetaria se ha empleado como un indicador de la función serotoninérgica sináptica en trastornos psiquiátricos como la depresión. Sin embargo, los estudios que han evaluado la correlación entre la depresión y los cambios en los niveles de serotonina plaquetaria han dado resultados contradictorios.

Por lo que respecta al precursor de la 5-HT, el triptófano (TRP), se ha sugerido que el cambio en los niveles de triptófano plasmático podría ser la causa de las alteraciones en los niveles de 5-HT, tanto en las plaquetas como en el cerebro, y asimismo se ha reportado una disminución de los niveles plasmáticos de TRP en pacientes con depresión.

Respecto al efecto que han ejercido los inhibidores selectivos de la recaptura de serotonina sobre la serotonina plaquetaria, se ha documentado que los inhibidores selectivos de esta recaptura inducen cambios en los niveles plaquetarios de esta amina.

Tomando en cuenta la controversia respecto a los niveles plaquetarios de 5-HT en pacientes deprimidos, y considerando además que a la fecha no se ha caracterizado el efecto de la depresión sobre los niveles de 5-HT y TRP en sangre en sujetos mexicanos, se decidió estudiar los niveles sanguíneos y plaquetarios de serotonina (5-HT) y triptófano (TRP) en pacientes deprimidos, y compararlos con los niveles de estas sustancias en sujetos sanos. Se estudió, además, el efecto del tratamiento antidepresivo con inhibidores selectivos de la recaptura de serotonina (fluoxetina o citalopram) sobre los niveles de 5-HT y TRP sanguíneos en pacientes deprimidos.

Material y métodos

Pacientes deprimidos: Los 30 pacientes incluidos en este estudio (24 mujeres y 6 hombres) se seleccionaron y evaluaron cuidadosamente. Como se consideró la influencia de la estacionalidad, al ingreso de cada paciente al estudio se le buscaba un control, para lo cual se le comparaba con un par por edad y sexo. En el caso de las mujeres, la sujeto control seleccionada se estudiaba ajustando la fase de su ciclo menstrual con el de la paciente en estudio.

Grupo control : El grupo control lo conformaron 30 sujetos sanos con una media de edad de 32.3 ± 10.8 años (24 mujeres y 6 hombres). Se confirmó que no hubieran sufrido ningún trastorno psiquiátrico y se aplicó el SCID-II para descartar cualquier alteración en el eje II. Todos los sujetos se mantuvieron libres de toda medicación durante por lo menos las tres semanas previas al estudio. Los controles mujeres se compararon de acuerdo con la fase del ciclo menstrual de las pacientes.

Después de recibir una explicación minuciosa, todos los sujetos participantes firmaron una carta de consentimiento informado para participar en este estudio. Los pacientes y los controles se examinaron físicamente con datos clínicos y de laboratorio (citometría hemática completa, pruebas bioquímicas, examen general de orina y pruebas de función tiroidea).

Los pacientes deprimidos recibieron, de forma abierta, un tratamiento farmacológico con base en inhibidores selectivos de la recaptura de serotonina (fluoxetina o citalopram) con la intención de lograr una remisión total de la sintomatología depresiva.

Cuando los pacientes presentaban una remisión de los síntomas depresivos, se les tomaba nuevamente una muestra de sangre para cuantificar los niveles sanguíneos y plaquetarios de 5-HT y TRP.

Análisis de 5-HT y TRP: El análisis de 5-HT y TRP en sangre total se realizó de acuerdo con el método descrito por Anderson; cada análisis se cuantificó después por cromatografía de alta eficiencia (HPLC).

Análisis estadístico: Por medio del análisis de varianza (ANOVA) de una vía, se determinó la existencia de diferencias estadísticamente significativas, y se utilizó la prueba de Tuckey HSD como prueba *post hoc*. En todos los casos se graficó la media ± el error estándar.

Resultados

Los resultados de laboratorio y gabinete (BHC, química sanguínea, función tiroidea [T3, T4 y TSH], examen general de orina y electroencefalograma) fueron normales, tanto en los pacientes deprimidos como en los sujetos control.

El número de plaquetas, la serotonina sanguínea, el contenido plaquetario de serotonina y la concentración de triptófano no mostraron diferencias en comparación con los sujetos control. Sin embargo, las concentraciones de serotonina sanguínea y plaquetaria fueron significativamente más bajas en pacientes deprimidos después del tratamiento antidepresivo.

Discusión y conclusiones

Las discrepancias entre este estudio y otros reportados en la bibliografía se explican en función de aspectos étnicos, fisiológicos y metodológicos, los cuales se discuten aquí.

El significativo decremento de las concentraciones de serotonina sanguínea y plaquetaria, producido por el tratamiento antidepresivo (fluoxetina o citalopram), puede ser consecuencia de la disminución de la recaptura de 5-HT por las plaquetas.

Considerando los resultados encontrados, podemos concluir que:

1. Los pacientes mexicanos no mostraron cambios en las concentraciones de serotonina en sangre ni en las plaquetas asociadas con la depresión.
2. Tampoco se encontraron cambios en las concentraciones de TRP en sangre asociada con la depresión.
3. El tratamiento con medicamentos antidepresivos inhibidores

selectivos de la recaptura de serotonina (fluoxetina o citalopram) se asocian con una disminución de la concentración de serotonina, tanto en sangre como en plaquetas, sin cambio en las concentraciones de triptófano en sangre.

Palabras clave: Depresión, 5-hidroxitriptamina, plaquetas, triptófano, antidepresivos.

INTRODUCTION

Since the mechanisms for a high-affinity serotonin uptake and storage (5-HT) in platelets are similar to those found in neurons (Stahl, 1977; Da Prada et al., 1988; Pletscher, 1987), platelets have been considered markers of the synaptic serotonergic function in psychiatric dysfunctions, such as depression (Stahl, 1977; Stahl et al., 1982; Quintana, 1992). However, most studies which have evaluated the correlation between depression and changes in platelet serotonin concentrations have shown controversial results. For instance, Wirz-Justice and Puhringer (1978) found an increase in the platelet serotonin concentration in patients suffering from bipolar depression compared to the one measured in control subjects; no differences were found in patients with unipolar depression. Sarrias et al. (1987) found a decrease in platelet serotonin in depressed subjects compared to control subjects. They proposed that neuronal serotonergic dysfunction is reflected in platelets. In turn, Quintana (1992) reported that platelet serotonin concentrations are diminished in patients with unipolar depression, whereas Mucck-Seler et al. (1991) reported higher platelet serotonin concentrations in depressed patients compared to controls. Karege et al. (1994) did not find any differences between depressed and control subjects.

On the other hand, results from the selective serotonin reuptake inhibitors (SSRIs) have been focused on the dysfunction of the cerebral serotonergic system involved in depression. Changes in the platelet serotonin concentrations have been documented using SSRIs (Menis et al., 1996; Blardi et al., 2002).

Plasmatic concentrations of tryptophan (TRP), the serotonin precursor, may be present in serotonin blood dysfunctions, as well as in the brain of depressed subjects. Decreased plasmatic concentrations of TRP have also been found in depressed patients in comparison to healthy subjects (Bovier et al., 1988; Karege et al., 1994).

Considering the literature controversy surrounding platelet serotonin concentrations in depressed patients, we studied serotonin and tryptophan concentrations in blood and platelets from depressed and control subjects to evaluate both a possible correlation with the severity of depression and SSRIs treatment (fluoxetine or citalopram).

METHODS

Depressed subjects

Thirty subjects, 24 women and 6 men, 18 to 45 years old (34 ± 11 years) were studied. These patients fulfilled the criteria for Major Depressive Episode of the Diagnosis and Statistics Manual of the American Psychiatric Association (DSM-IV American Psychiatric Association, 1994). The symptoms severity was evaluated with the Hamilton's Scale for Depression (HSD) (Hamilton, 1960), as well as with the Beck's Inventory for Depression (IBD, Beck, 1961). All the selected patients scored higher than 22 points in HSD. Depressive patients had no pharmacological treatment during the 30 days prior to the study, and took the Structured Interview for Personality Dysfunctions, SCID-II, to discard any personality disorder associated to depression. To avoid seasonal variations, patients were matched with their controls by age and sex. The women were also paired according to their menstrual cycle phase. The Mini-International Neuropsychiatric Interview (MINI), in its validated Spanish version (Heinze et al., 2000), was applied to the subjects by one of the investigators. Subjects with any neurological or psychiatric dysfunction were excluded, including alcohol and psychoactive substance dependence, as well as pregnancy. Patients suffering from depression received pharmacological treatment under clinical staff supervision using selective serotonin reuptake inhibitors (either fluoxetine or citalopram in a dose of 20 or 10 mg/day, respectively). Patients with a complete remission of depression symptoms (defined as a score not higher than 5 points in the Hamilton's scale, and lower than 7 points in the Beck's scale) were asked for a blood sample to measure platelet and blood concentrations of 5-HT and TRP. Patients were weighted before the treatment and after their improvement.

Control subjects

The control group was integrated by 30 healthy subjects, 24 women and 6 men, with an average age of 32.3 ± 10.8 years. Participants were recruited from the overall Mexican population, interviewed by a psychiatrist, and evaluated with the structured interview MINI, and the SCID-II to discard any psychiatric personality disorder diagnose. None of them had received any pharmacological treatment during the three weeks prior to the study. Control and depressed women were paired according to the menstrual cycle phase.

All participants received a detailed explanation of the study, and those who voluntarily accepted the stipulations signed an informed consent document. Control and patient subjects were clinically examined and studied with routine laboratory tests (blood count, blood chemistry, urinalysis, and thyroid function test).

Blood sample procedures

Blood samples were collected during the morning, between 7:30 and 9:00, in Vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ) containing a 250 µl 10% EDTA (K_3) solution as anticoagulant. An aliquot of 250 µl was placed in 1.5 ml plastic microtubes for 5-HT and TRP analysis in whole blood. Sample preparation was performed in agreement with Anderson (1987). Briefly, 250 µl of blood and 50 µl of ascorbic acid were mixed during 10 seconds with 50 µl of a solution of 3.4 M $HClO_4$. The mixture was allowed to rest during 10 minutes at 0-4°C, and centrifuged for 5 minutes at 7,500 x g. The supernatant was filtered through a 0.45 µm filter, and 50 µl of the deproteinized sample was injected in the chromatograph.

Chromatographic system

Serotonin and tryptophan were determined by high performance liquid chromatography (HPLC), using a Novapak column. The mobile phase consisted of buffer/acetonitrile (95:5 v/v). The buffer constitution was: 12.6 mM citric acid; 11.60 mM $(NH_4)2HPO_4$, 2.54 mM sodium octylsulphonate, 1.11 mM EDTA disodic salt, and 3.32 mM dibutyl amine phosphate. The pH was adjusted at 3.17 with NaOH (2N) after the addition of acetonitrile. The mobile phase was pumped in isocratic flow at 1.0 ml/min.

HPLC equipment consisted of a Waters pump 510 (Milford, MA, U.S.A), a Waters 710B WISP autosampler, a Waters packed with I insert Novapak C18 guard column, and a Novapak C18 (3.9 x 150 mm) column. A Waters 470 fluorescence detector was used, with an excitement wave longitude of 278 nm, and an emission of 335 nm. The eluent was filtered through a filter of 0.22 µm. Two programs of gain of 0-6 min were used: one with a gain X 1 and another of 6-13 min with a gain X 100. Retention time for the TRP was 5 minutes, and of 7.84 minutes for the 5-HT. The intra-assay variation coefficient was 1.77% for TRP (n = 20, 8.55 µg/ml) and 5.30% for 5-HT (n=20, 40.65 ng/ml). The inter-assay variation coefficient was 3.08% for TRP (n = 5, 8.98 µg/ml), and 5.24% for 5-HT (n = 4, 43.75 ng/ml).

Statistical analysis

The differences were statistically determined with an analysis of variance (ANOVA), with the assistance of the SPSS 12.00 (Statistical Software by SPPS Inc.).

RESULTS

Results from laboratory tests, such as blood count, blood chemistry, thyroid function (T3, T4 and TSH) and urinalysis, were normal in depressed subjects, as well as in healthy volunteers. There were not any significant differences between the values of these two groups (data not shown).

At the beginning of the study, patients showed higher average rates of depressive symptoms (HAMD 25.21 ± 0.62; BDI 25.6 ± 1.74), compared to control subjects (HAMD 1.25 ± 0.35; BDI 3.3 ± 0.78) (figures 1 and 2).

The pharmacological treatment with fluoxetine or citalopram induced symptom remission according to Hamilton (HAMD 3.3 +/-1.25) and Beck (BDI 4.23 +/-1.07) scales, wich were scored at the end of the study. The antidepressant treatment did not produce any significant changes in patients weight (figure 3).

Blood platelets

Although the platelet number was slightly lower in depressed patients in comparison with control subjects,

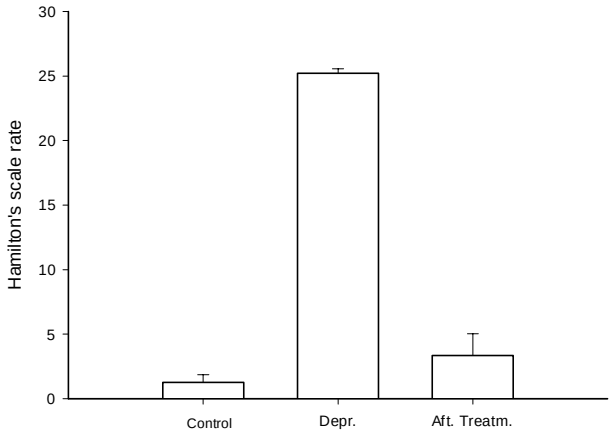

Fig. 1. Hamilton's scale score averages in controls and patients, before and after the antidepressant treatment. Bars represent ± standard error.

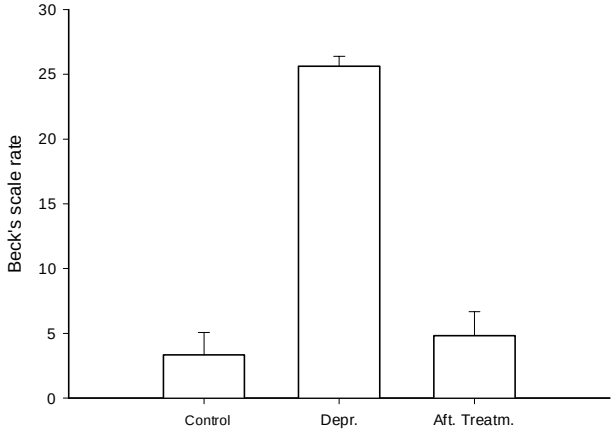

Fig. 2. Beck's scale score averages in controls and patients, before and after the antidepressant treatment. Bars represent ± standard error.

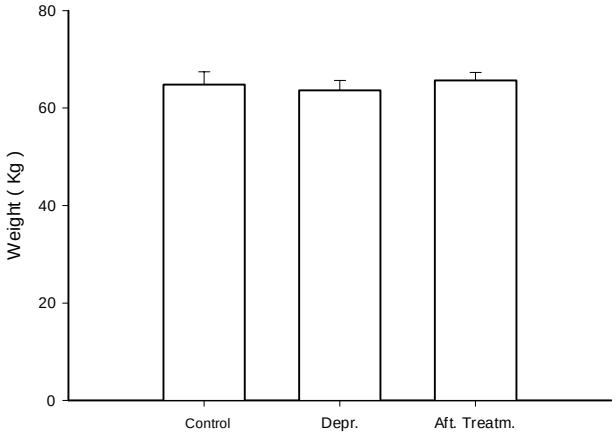

Fig. 3. Weight averages in control and patients before and after the antidepressant treatment. Bars represent ± standard error.

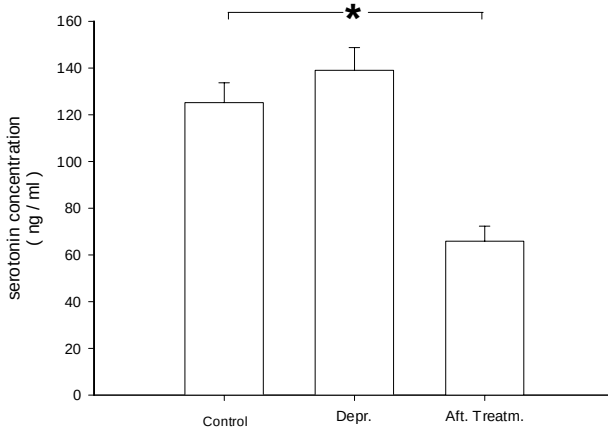

Fig. 5. Serotonin concentration in the whole blood preparations. Bars represent ± standard error, and the asterisk represents significant differences ($p < 0.05$).

the difference was not significant ($F_{2,74} = 3.64$; $P = 0.061$). On the other hand, the antidepressant treatment did not produce significant changes in the number of platelets in patients ($F_{2,74} = 2.522$; $P = 0.087$) (figure 4).

5-HT concentration in blood

The average of blood serotonin concentration in depressed patients was slightly higher compared to controls (figure 5), but the difference was not significant ($F_{2,74} = 0.581$; $P = 0.449$). At the end of the antidepressant treatment the serotonin concentrations were significantly lower in patients ($F_{2,74} = 11.281$; $P < 0.000$) than the initial concentrations.

Platelet content of 5-HT

Similarly to blood serotonin, the platelet content of serotonin did not showe significant differences ($F_{2,74} = 2.529$; $P = 0.117$) between depressed patients and control subjects (figure 6). However, at the end of the antidepressant treatment, the platelet serotonin concentrations were significantly lower ($F_{2,74} = 13.564$; $P < 0.000$), compared to the initial concentrations of depressed and control subjects.

Blood tryptophan concentration

The blood tryptophan concentrations (figure 7) did not showe any differences between depressed patients and control subjects ($F_{2,73} = 0.213$; $P = 0.646$). However, contrarily to the serotonin concentrations, the blood TRP concentration did not change after the antidepressant treatment ($F_{2,73} = 0.104$; $P = 0.901$).

DISCUSSION

In this study, 5-HT and TRP concentrations were measured both in blood and platelet preparations to evaluate possible differences between depressed patients and healthy volunteers. As far as we know, this is the first study to evaluate these aspects in Mexican subjects, together with the effect of antidepressant treatment on 5-HT and TRP concentrations.

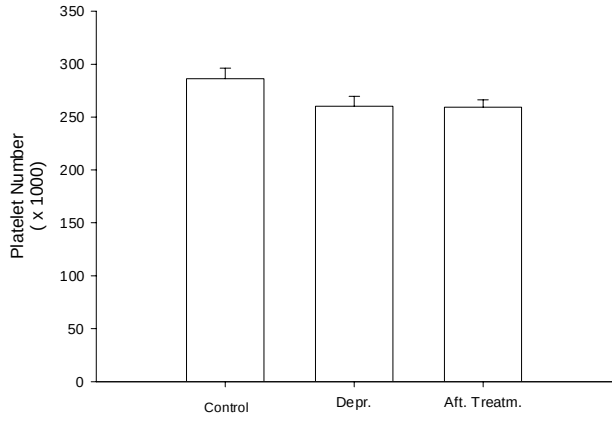

Fig. 4. Amount of platelets in the whole blood preparation. Bars represent ± standard error.

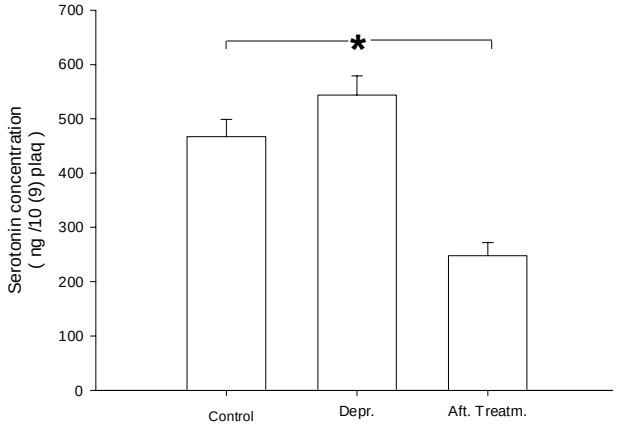

Fig. 6. Serotonin concentration in platelets. Bars represent ± standard error, and asterisk represents significant differences ($p < 0.05$).

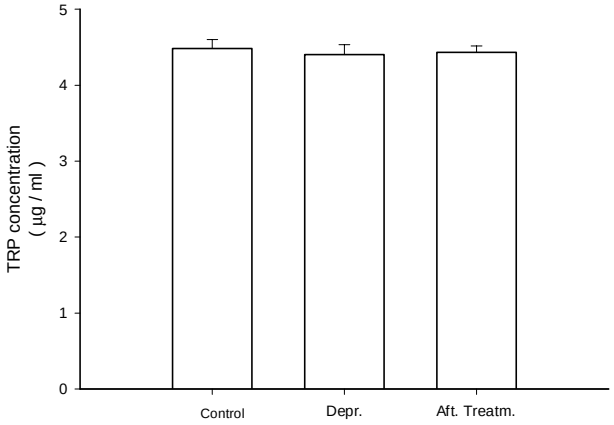

Fig. 7. Tryptophan concentration in the whole blood preparations. Bars represent ± standard error.

Depressed patients showed significantly higher depressive symptom scores than control subjects when evaluated both with the Hamilton's scale (figure 1) and the Beck's scale (figure 2). The antidepressant treatment elicited a significant reduction in the symptoms severity, without affecting patients' weight (figure 3). Regarding this, it has been documented that the weight increment relates more often to paroxetine than to fluoxetine (Calil, 2001). We believe that this may explain why no significant weight changes were found in patients. Platelet number by blood milliliter was similar both in patients and controls, and antidepressant treatment did not produce any changes in the number of platelets in the depressed patients group. The serotonin concentration in depressed patients was similar to the one in control subjects. This means that none of the groups presented any changes in serotonin concentration, platelets or blood preparations.

Our results differ from previous studies like those by Sarrias et al. (1987), Quintana (1992), or Cleare (1997), who reported lower platelet 5-HT concentrations in depressed patients when compared to controls. However, our results coincide with the reports of Mann et al. (1992); Karege et al. (1994); Mûck-Seler et al. (1991 and 1996) and Hughes et al. (1996), who did not find differences between depressed patients and controls.

Discrepancies between our study and those found in the literature studies can be explained from three different approaches. The first one involves ethnic factors which have been considered in studies by Cuccaro et al. (1993), Cook et al. (1995), and Hughes et al. (1996). In particular, Hughes et al. (1996) compared children and adolescents with mood disturbances with their respective controls, finding that Afro-American patients had higher 5-HT blood concentrations than the Caucasian ones. However, they did not find differences between patients with mood disturbances and their controls in the Afro-American ethnic group, while the Caucasian patients showed differences in blood serotonin concentrations related to depression. These authors have proposed that race is a critical variable that should be controlled in biological markers studies. The present study is the first one of this kind carried out in Mexico; therefore, further investigations concerning racial aspects in Mexican population are needed.

The second factor is physiological. In this regard, Karege et al. (1994) mention that several factors may be involved in the control of 5-HT storage by platelets, such as serotonin synthesis, uptake, release, and metabolism mechanisms. Any alteration in these processes could adversely affect serotonin platelet content.

The third aspect is methodological. Cleare (1997) studied 17 depressed patients, including four patients with suicide attempt history, that could have influenced his results. Mann (1992) had previously published that depressed patients with suicidal attempt had lower 5-HT blood and platelet concentrations than non-suicidal depressed patients. In this regard, patients in our study were carefully selected and evaluated with clinimetric instruments (MINI and SCID-II) by two physicians to exclude the bias of personality dysfunctions, suicidal attempts, or any other psychiatric disorders.

Regarding tryptophan concentrations, we did not find differences in blood either in control subjects or depressed patients, not even when these patients were given an antidepressant treatment (figure 7).

Blood tryptophan concentration is known as an indicator of tryptophan converted to serotonin in the central nervous system; this biological marker could be used as a reference of the CNS serotonergic activity (Quintana et al., 1992). However, our results did not support this assumption. Likewise, other authors have not found differences between TRP concentration in depressed patients and control subjects (Russ et al., 1990; Karege et al., 1994; Aymard et al., 1993).

On the other hand, the selective inhibitors of serotonin reuptake have showed their antidepressant effects. In this study, blood and platelet 5-HT concentrations were found to diminish after a fluoxetine or citalopram treatment. This finding agrees with results from Kremer et al. (1990); Celada et al. (1992); Karege et al. (1994); Blardi et al. (2002), and Castrogiovanni (2003), who reported a decrease of the serotonin concentrations in blood and in platelets, induced by the antidepressant treatment.

Calil (2003) mentioned that hypothetical mechanisms for the remission of depressive symptoms using SSRIs included both the increment in the synapse of the serotonergic signal as a consequence of the inhibition of the uptake system, and the reduction of the availa-

bility of serotonin in the synapses, as a consequence of the pharmacologically diminished serotonin uptake. Other mechanisms may be the SSRIs secondary effects in other neurotransmitter systems, such as the noradrenergic, dopaminergic, cholinergic, and GABAergic, which are associated with several clinical symptoms, as well as with differences in patients' biological and cognitive sensitivity.

The significant decrease produced by the antidepressant treatment in blood and platelet serotonin concentration may be a consequence of the action of SSRIs, due to a 5-HT diminished uptake by the platelet. Menys et al. (1996), Spreux-Varoquaux et al. (1996) and Blardi et al. (2002) have suggested that platelet serotonin measurement may be useful as a possible model to study the clinical response in depressed patients.

In our study, depressed patients treated with SSRI improved their depressive symptoms, which is common in these patients without any other psychopathology. However, in depressed patients having other psychiatric disturbances, such as personality dysfunction, SSRI antidepressant treatment is not satisfactorily effective (Papakostas et al., 2003).

CONCLUSIONS

1. Blood and platelet 5-HT concentrations were not different between depressed patients and healthy volunteers.
2. Blood TRP concentrations were not different between depressed patients and healthy volunteers.
3. SSRIs (fluoxetine or citalopram) used in the treatment of depressed patients induced a significant decrease in blood and platelet content of 5-HT, and had no effect in TRP concentrations.

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