

Functional Change of Brain Serotonergic Activity and Free Tryptophan in the Plasma of Depressed Women

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Abstract

The main objective was to show the decrement of serotonergic brain activity in depressed women, through the analyses of the slope amplitude of N1/P2 components of the auditory-evoked potentials (AEP), and the measurement of the L-tryptophan free fraction in plasma (FFT). This cross-sectional study was carried out in 60 women, 30 depressed and 30 normal controls. Both groups were measured FFT, glucose, and neutral amino acids (NAA) levels; besides performing AEP to analyses the N1/P2 slope amplitude. It was found a lengthening in the slope amplitude of N1/P2 components of AEP in the group of depressed women, and despite that the level of FFT was low, there were no changes between bound fraction and the total L-Trp. The former suggests a decrease in serotonergic brain activity in the group of depressed women. Otherwise, since the auditory cortex response to sound is regulated by serotonergic innervation, it was expected a change in the behavior of AEP in the group of depressed patients. Thus, the slope amplitude of N1/P2 components of the AEP and the measurement of FFT have proved to be a good clinical indicators of the serotonergic neurotransmission state in the brain of depressed patients, and in another clinical conditions where brain serotonin is involved.

Keywords

Depression, Auditory-Evoked Potential (N1/P2) Component, Brain, Serotonin, L-Tryptophan

1. Introduction

Depression triggers a strong impact on general population morbidity and leads

to a high rate of disability worldwide (Kessler & Bromet, 2013), taking into account that in Mexico, its prevalence reaches a 4.8% between the 18 and 65 years of age, only outweighed by anxiety disorders (Medina-Mora et al., 2005; Wagner et al., 2012; Berenzon et al., 2013). Notwithstanding its diagnosis is clinical and based on the parameters established by the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-IV) (American Psychiatric Association, 1994), the neurophysiopathological basis of depression has not yet been described. However, there are some hypotheses related to the dysfunction of some networks and neurotransmission neuronal systems inside the limbic area, and the cortex; which are based on different polymorphisms that may lead to metabolism dysfunction, and transport alterations of monoamines, serotonin, dopamine, norepinephrine, glutamate, and gamma-amino-butyric acid (GABA) along these systems (Nestler et al., 2002; Meltzer, 1990; Dunlop & Nemeroff, 2007; Nutt, 2006; Sullivan et al., 2000; Lohoff, 2010; Pehrson & Sanchez, 2014). Neurogenesis also influence the development of the disease (Jedynak et al., 2007), besides genetics, environment influence (Sullivan et al., 2000), and the role inflammation plays (McNally et al., 2008; Patel, 2013). Thus, depression must not be viewed as a single disease, but as a syndrome triggered by different causes and physiopathology (Nestler et al., 2002). Different attempts have been made to establish several subtypes of depression, based on certain groups of symptoms (Akiskal, 2000; Blazer, 2000); however, these subtypes are based solely on symptomatic differences, and there is as yet no evidence that they reflect different underlying disease states.

The scientific evidence of serotonergic activity in the physiopathology of depression that has been reported in recent years, has led to the therapeutic use of selective serotonin reuptake inhibitors in the depressed patient (Mann, 1999; Gijsman et al., 2004; Margoob et al., 2008; Carr & Lucki, 2011; Berhan & Barker, 2014; Morrissette & Stahl, 2014). Likewise, different pathophysiological changes have been reported, such as the decrease in the serotonin level inside the brainstem, and a decrease in 5-hydroxyindoleacetic acid in the cerebrospinal fluid; increased clearance of L-Trp during major depressive episodes, in contrast with a minor plasma level (Banki et al., 1981; Stanley et al., 1985; Ferrier et al., 1986); and changes in the expression of various serotonergic receptors (Carr & Lucki, 2011; Nagayama et al., 1991; Stockmeier et al., 1997) along with an increased neuroendocrine activity (López et al., 1998; Parker et al., 2003).

This study is based on the hypothesis that sustains that depressed women have a significant decrease in brain serotonergic activity, which could be demonstrated through the analyses of the slope amplitude of N1/P2 components of the auditory-evoked potentials (AEP), and the measurement of the L-tryptophan free fraction in plasma (FFT) (Hegerl & Juckel, 1993; Juckel et al., 1997; Manjarrez et al., 2001; Manjarrez et al., 2005a; Manjarrez et al., 2005b). Recent results show that patients with type 1 and type 2 diabetes (with or without depression) and patients who develop depression after myocardial infarction present a significantly higher slope of the amplitude/stimulus function (ASF) of the N1/P2

component obtained at various intensities of the auditory stimuli, reflecting a low brain serotonergic activity (Manjarrez et al., 2006; Manjarrez et al., 2007; Manjarrez-Gutierrez et al., 2009; Manjarrez-Gutierrez et al., 2013). On the contrary, low-intensity dependence is assumed to result from high serotonergic function as observed in intrauterine growth-restricted infants and rats (Manjarrez et al., 2001; Manjarrez et al., 2005a). Therefore, the ASF slope of the N1/P2 component of IDAEPs and the free fraction of L-tryptophan (FFT) have been used as indicators of central serotonergic activity in humans (Manjarrez et al., 2005a; Manjarrez et al., 2006; Manjarrez et al., 2007; Manjarrez-Gutierrez et al., 2009; Manjarrez-Gutierrez et al., 2013).

2. Patients and Methods

This study was approved by the Research and Ethics Committees of the Specialties Hospital of the National Medical Center (IMSS, Mexico City). All women provided informed consent after receiving a detailed explanation of the involved procedures. A cross-sectional study was carried out in 60 women (aged 47 - 52 years). Two groups were formed. The first group included 30 patients with depression according to the DSM-IV criteria. None of the depressed patients' received specific treatment. They did not have neurological events, cardiovascular complications, or signs of brain or other psychiatric disorders. The use of medications such as sedatives, antidepressants or neuroleptics, were considered as an exclusion criterion. On the other hand, 30 normal women within a similar age range served as a control group. All patients in this study had normal hearing, with a perception up to 20 dB confirmed by an audiologist, and also normal cognitive functions. Patients consumed a regular diet (22 - 26/kcal/kg/day).

3. AEPs Recording and Analysis

During the recording of IDAEPs, each subject sat in a comfortable chair in an electrically shielded and sound-attenuated room, adjacent to the recording apparatus (Viking 4, Nicolet). IDAEPs were recorded with two channels referred to as Cz. AgCl electrodes were used (EEG disk electrode NE-101, 10 mm diameter). It were applied two hundred clicks (1.5 kHz, 100 ms duration with 10 ms rise and 10 ms fall time, interstimulus interval between 1000 and 1500 ms), with three intensities to assess the intensity dependence (70, 90 and 103 dB). Each of the intensities was separately applied, binaurally in a sequential form through headphones. Data were collected with a sampling rate of 1000 Hz and an analogue bandpass filter (0.1 Hz - 150 Hz). Prestimulus periods (200 ms) and post-stimulus periods (500 ms) were evaluated with 200 sweeps for each intensity increment. For artifact suppression, all trials were automatically excluded from averaging if the voltage exceeded 50 μ V in either of the two channels at any time during the averaging period. The X-Y graphs of the IDAEP were examined and prominent peaks identified and measured using specific software (Viking 4, Nicolet). Plots shown in **Figure 1** are representative examples of IDAEP long latency waves obtained by sequential stimulations of 70, 90 and 103 dB from a

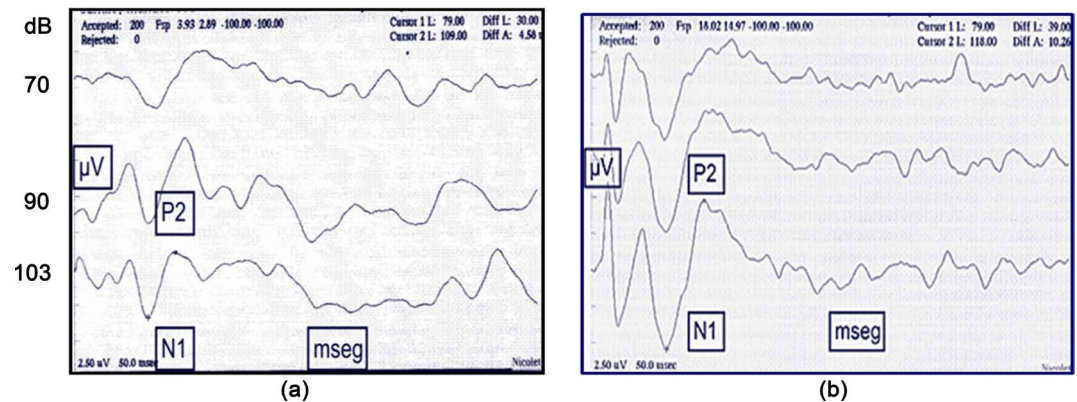


Figure 1. Illustrative examples of cortical auditory evoked potentials (200 averaged responses) obtained at stimulation of 70, 90 and 103 dB sound pressure level in a control woman (a) and a patient with depression (b) peak-to-peak amplitude of the N1/P2 component was measured in this study.

control subject (A) and a patient with depression (B). Latencies in milliseconds and amplitudes in μV were also calculated. The amplitude of the segment N1/P2 of the IDAEP was considered as the sum (in μV) between the crests of the waves N1 and P2. The N1 component of the individual dipole source is measured as the negative peak within 60 - 120 ms, and the P2 component is measured as the positive peak within 110 - 210 ms (Hegerl & Juckel, 1993; Juckel et al., 1997, Manjarrez et al., 2001; Manjarrez et al., 2005a). Therefore, it is accepted that these components are representative of the auditory cortex integrative function (Semple & Scott, 2003).

4. Biochemical Assays

Ultrafiltered plasma fractions were obtained using Nanosep 30K membranes (Omega; Pall Life Science, Ann Arbor, MI) in which the FFT was measured. The high-performance liquid chromatography (HPLC) fluorescent method of Peat et al. (Peat & Gibb, 1983) was used to quantify the FFT and the total L-Trp. The difference between these two was considered the fraction bound to albumin. Plasma albumin was determined by the method of Doumas et al. (Doumas et al., 1971). Glucose-oxidase method was used to quantify plasma glucose (Bentley, 1963), glycated hemoglobin and NAA by HPLC (Cole et al., 1978; Einarsson et al., 1983). For free fatty acid (FFA) levels assessment it was applied the Wako NEFA C test kit which uses an in vitro enzymatic colorimetric method.

5. Statistical Methods

Results are presented as mean \pm standard deviation. Differences between mean values were analyzed with the Student *t*-test and Levene tests with a level of significance accepted at $P < 0.05$. Peak-to-peak amplitude of N1/P2 component was measured at 70, 90 and 103 dB stimulus intensities, and the relationship between the N1/P2 component amplitude related to the auditory stimulus intensity (ASF slope) was estimated using linear regression analysis for each study group. We compared ASF slopes using Student *t*-test; $P < 0.05$ was considered significant.

6. Results

A group of 60 women with an age average of 48.75 ± 9.2 years were studied. Patients belonged to the depressed group were significantly younger than those from the control group ($P < 0.001$) and had a clinical evolution of 16 ± 10.0 months at the time the study was carried out. They also showed overweight ($P < 0.05$) and a normal level of plasma glucose. There were no changes in albumin, free fatty acids, glycosylated hemoglobin and NAA (**Table 1** and **Table 2**). The free fraction of L-tryptophan was significantly decreased in depressed women in relation to controls ($P < 0.001$). There were also no changes in the values of total L-Trp, FFT/total L-Trp and FFT/NAA (**Table 3**).

The most important clinical parameter studied in these patients was the intensity-dependence AEPs represented by the N1/P2 component. Notice that the ASF slope ($-4.76 + 1.28$ intensity, $r^2 = 0.92$) in the depressed patients showed a significant increase compared to controls ($-2.69 + 0.62$ intensity, $r^2 = 0.95$) ($P < 0.001$) (**Figure 2**). Although there was no significant correlation observed between ASF slope and the free fraction of L-Trp (results not shown), both changes

Table 1. Clinical and biochemical data in women with depression and controls.

	Controls (n = 30)	CV	Depression (n = 30)	CV
Age	47.0 ± 10.0	0.21	$41.0 \pm 8.0^*$	0.19
Body mass index	23.5 ± 5.0	0.21	$26.9 \pm 5.0^{\ddagger}$	0.18
Waist circumference (cm)	73.0 ± 6.0	0.08	$89.8 \pm 14.0^*$	0.15
Time of evolution (months)	--	--	16.0 ± 10.0	0.62
Beck	3 ± 2	0.66	25 ± 10.0	0.40
MADRS	--	--	24 ± 10.0	0.41
Glucose (mg/dL)	86.5 ± 7.0	0.08	91.3 ± 10.0	0.10
Hb _{A1C} (%)	5.1 ± 0.4	0.07	5.5 ± 0.6	0.10
Free fatty acids (mmol/L)	0.82 ± 0.10	0.12	0.78 ± 0.09	0.10
Albumin (g/dL)	6.20 ± 0.35	0.5	6.09 ± 0.21	0.03

Values are given means \pm SD. All determinations were done in duplicate sample. Differences were determined by Student's *t*-test. * $P < 0.05$, $\ddagger < 0.001$. CV = coefficient of variation.

Table 2. Plasma concentration of neutral amino acids in women with Depression and Controls.

	Controls (n = 30)	CV	Depression (n = 30)	CV
Valine	327 ± 23.5	0.07	345 ± 25.5	0.07
Isoleucine	222 ± 17.1	0.07	214 ± 14.2	0.06
Leucine	346 ± 22.8	0.06	332 ± 11.8	0.03
Phenylalanine	187 ± 15.0	0.08	164 ± 21.2	0.12
Tyrosine	187 ± 15.0	0.09	168 ± 14.8	0.08
Σ NAA	187 ± 15.0	0.07	1223 ± 87.5	0.07

Values are given as means \pm SD (μ mol). All determinations were done in duplicate samples. Differences were determined by Student's *t*-test. P = Not significant. CV = coefficient of variation.

Table 3. Plasma concentration of L-Tryptophan in women with Depression and Controls.

	Controls (n = 30)	CV	Depression (n = 30)	CV
Free fraction (FFT)	8.4 ± 1.1	0.13	5.9 ± 0.9*	0.15
Albumin bound	31.6 ± 5.1	0.16	32.3 ± 5.0	0.15
Total (T)	40.0 ± 5.3	0.13	38.2 ± 4.0	0.10
FFT/T ratio	0.168 ± 0.020	0.11	0.153 ± 0.02	0.13
FFT/NAA ratio	0.006 ± 0.001	0.20	0.004 ± 0.001	0.20

Values are given as means ± SD (µmol). All determinations were done in duplicate samples. Differences were determined by Student's *t*-test. *P< 0.001. CV = coefficient of variation.

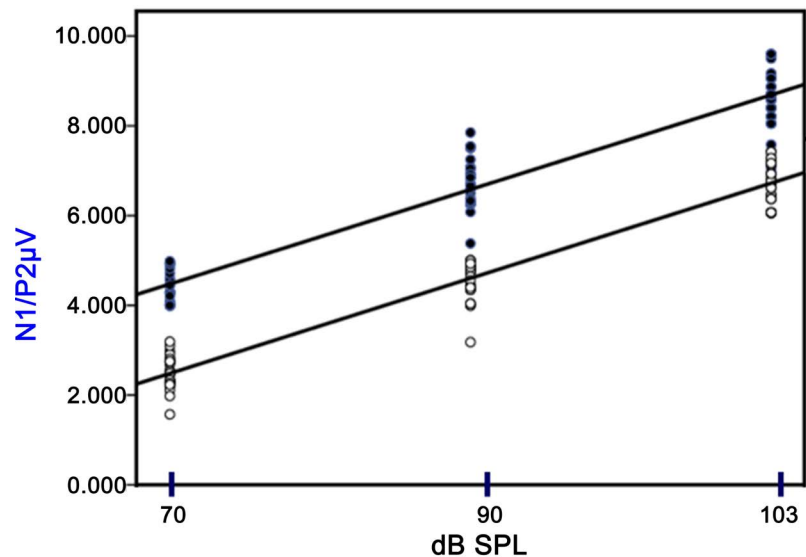


Figure 2. Multiple regression analyses and Scatter diagram. ○, Control women, ASF slope = $-2.69 + 0.62$ intensity, $r^2 = 0.95$; ●, Depression women, ASF slope = $-4.76 + 1.28$ intensity, $r^2 = 0.92$.

indicate low brain serotonergic tone in women with depression. Additionally, there were no changes in latencies of N1 and P2 in both groups.

7. Discussion

The main objective of this study was to show the decrement of serotonergic brain activity in depressed women, through the analyses of the slope amplitude of N1/P2 components of the auditory-evoked potentials, and the measurement of the L-tryptophan free fraction in plasma. Analyses of N1/P2 components of the AEP was based on previous findings that show, this slope reflect changes in cortical activity due to abnormalities in serotonergic neurotransmission (Hegerl & Juckel, 1993; Juckel et al., 1997; Manjarrez et al., 2001; Manjarrez et al., 2005a; Manjarrez et al., 2006; Manjarrez et al., 2007; Manjarrez-Gutierrez et al., 2009; Manjarrez-Gutierrez et al., 2013). Biochemical results showed a significantly low level of the free fraction of L-Trp in the depressed women group; fact that initially suggests a low transport of tryptophan to the brain and as a result, a low synthesis of serotonin which leads to a serotonergic activity reduction. How-

ever, it can also be explained by the preferential use of L-Trp by other metabolic pathways such as the kynurenic and nicotinic acid or also as a result of a hyperactivity of the hepatic tryptophan oxygenase, which catabolize the L-Trp (Badawy, 1977).

The amplitude/stimulus intensity function (ASF) of the N1/P2 component of the AEP has been proposed as an indicator of the activity of serotonergic neurons on the primary auditory cortex (Hegerl & Juckel, 1993; Juckel et al., 1997) where a low activity of serotonergic neurons leads to a high intensity dependence with higher N1/P2 amplitudes (Manjarrez et al., 2006, Manjarrez et al., 2007; Manjarrez-Gutierrez et al., 2009; Manjarrez-Gutierrez et al., 2013).

Our results as well as those of the group of Hegerl and Juckel (Hegerl & Juckel, 1993) strongly suggest a functional relationship between brain serotonergic activity and the N1/P2 changes to the auditory cortex responses to specific stimuli. Thus, changes in N1/P2 component of the intensity dependence of AEP, could reflect a cortical impaired activity as a result of brain serotonergic activity dysfunction. This remarkable fact is meaningful, since the component of the auditory cortex electrical activity (N1/P2) depends of the spatial and temporal integration of several neuronal processes. In fact, the electrical dipole source analyses have lead to the identification of two major components in each hemisphere (Hegerl & Juckel 1993; Juckel et al., 1997): 1) A tangential dipole source which reflects the activation of the primary auditory cortex; and 2) A radial dipole which is results of the activity in the secondary auditory cortex. Since N1/P2 is also induced in children and detected in the corresponding auditory projections on the scalp, it seems reasonable that cortical waves reflect the integration of the auditory activity in both, children and adults (Semple & Scott, 2003). On these bases, any dysfunction in the auditory cortex activity that lead to a change in the N1/P2 component reflects the activity of a regulatory central mechanism of sensory sensitivity. Departing from this hypothesis, a lower cortical activity would reflect a higher activity of this mechanism, triggered in order to protect the structure from sensory overload; whereas an elevation in cortical activity would be associated with a failure of the process (Ehlers et al., 1991; Von Knorring et al., 1978). Thus, in this study the increment in the ASF slope demonstrated in the group of depressed women in contrast to controls, could be the result of a detriment in the sensory cortical regulatory mechanism. As a matter of fact, a number of authors have suggested the brainstem as the source of this regulatory mechanism, which could be represented by the serotonergic system (Jacobs & Azmitia, 1992).

Based on our biochemical and electrophysiological results, we propose that the abnormal response of the auditory cortex in the group of depressed women could be the result of a failure in serotonergic tone because of a detriment on serotonin synthesis. At the level of neurons and taking into account that this process starts at the primary auditory cortex, which owns GABAergic circuits innervated by serotonergic neurons (Jacobs & Azmitia, 1992; Zhou & Hablitz, 1999), the physiopathology of the failure suffered by the serotonergic tone, could

be explained by the inhibition triggered by the GABA system. On the contrary, a reduction in GABAergic function in response to environmental stimuli could increase cortical activity, suggesting that these patients are more susceptible to auditory stimuli that may lead to behavioral changes and psychiatric disorders. On the whole, all these findings seem to be clinically relevant, since they explain metabolic and electrical changes that may play an essential role in the pathophysiology of depression. Therefore, we propose the use of the intensity dependence of AEPs (N1/P2 component) along with the measurement of plasma free fraction of L-Trp as noninvasive clinical indicators of brain serotonergic neurotransmission, methods that could be useful to differentiate depression states from a normal behavior.

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Conflicts of Interest

The authors declare no conflicts of interest.

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