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ORIGINAL PAPER

GABA and Homovanillic Acid in the Plasma of Schizophrenic and Bipolar I Patients

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Abstract We have determined the plasma (p) concentration of gamma-aminobutyric acid (GABA) and the dopamine metabolite homovanillic acid (HVA), and the pHVA/pGABA ratio in schizophrenic and bipolar patients. The research was undertaken in a geographic area with an ethnically homogeneous population. The HVA plasma concentrations were significantly elevated in the schizophrenic patients compared to the bipolar patients. The levels of pGABA was significantly lower in the two groups of patients compared to the control group, while the pHVA/pGABA ratio was significantly greater in the both groups of patients compared to the controls. As the levels of pHVA and pGABA are partially under genetic control it is better to compare their concentrations within an homogeneous population. The values of the ratio pHVA/pGABA are compatible with the idea of an abnormal dopamine-GABA interaction in schizophrenic and bipolar patients. The pHVA/pGABA ratio may be a good peripheral marker in psychiatric research.

Keywords Plasma · Homovanillic acid · Gamma-aminobutyric acid · Schizophrenia · Bipolar disorder

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Introduction

For the past decades the psychiatric diagnosis has been standardized based on patient features of a phenomenological nature, given that the biological basis for most syndromes, although recognized in its existence, remains unknown. Therefore, the resulting categories are mere hypotheses put across with little knowledge of the brain alterations that sustain them. In these circumstances, clinical and scientific attempts to orient research towards the discovery of the mechanisms that accompany psychiatric diseases meet great difficulties. Psychotic destabilization, depending on the interaction of diverse genes with different circumstances, co-exists with diverse phenotypes. For example, here prevail, (to a greater or smaller degree): alterations in the course of thought, affective symptoms or cognitive disorders. Consequently, to facilitate the advance in neurobiological investigation in psychiatry it is absolutely necessary to identify markers that may help define endophenotypes which objectively sub-group psychiatric patients. It is evident that we lack such markers [1].

Direct investigation of the human brain is obviously difficult; and, for ethical reasons as much as for practical ones, human neurobiological research is mostly limited to indirect, noninvasive methods. One of these methods is to determine the plasma concentration levels of some neurotransmitters and their metabolites. Although plasma

metabolites come from the central nervous system as well as from the periphery, in suitable experimental conditions they reflect central changes [2, 3]. Significant correlations between peripheral and central changes are possible because the central contribution is sufficient to dominate a statistical relation, or because the central and peripheral pools, under genetic control, are affected in a co-relative way [4]. An example of interest to our study is homovanillic acid (HVA), dopamine's main metabolite. Haloperidol, which blocks central and peripheral dopamine receptors, elevates the plasma concentration of homovanillic acid (pHVA); whereas domperidone, being a powerful antagonist in the peripheral receptors of dopamine but not penetrating into the brain, does not elevate pHVA [5]. The determination of plasma levels of gamma-aminobutyric acid (pGABA) has also been suggested as an index of cerebral GABA activity [6, 7]. The concentrations of GABA in the plasma and in the brain change in a proportional and correlated way after pharmacological manipulation [7–11].

The plasma concentration of both substances has been related to psychiatric disorders. Two decades ago several groups, among them our own, demonstrated the existence of a relationship between the pHVA concentration and the response to neuroleptic treatment in schizophrenic patients, based on the dopaminergic hypothesis of the schizophrenic process. The clinical improvement correlated positively with the decrease of pHVA [12–15]. Furthermore, a greater initial increase of pHVA in response to neuroleptic treatment was a predictive factor of good clinical evolution [13]. In general these works were confirmed later, including, on occasion, the determination of other metabolites [16, 17]. The plasma concentration of homovanillic acid also proved to be a useful tool in other pathologies such as the Hungtinton disease [18].

The studies of catecholamines metabolites in plasma in patients with BPD have given contradictory results, although high values of pHVA and pMHPG (3-methoxy-4-hydroxyphenylethylenglycol) have been generally found before treatment [19, 20]. In other series of studies concentrations of pHVA or pMHPG, or their changes during treatment, have been related to clinical evolution [20–24].

GABA's cerebral activity has also been related to several neuropsychiatric disorders. Depression, panic attacks, alcohol dependency or post-traumatic stress have been associated to a reduction of GABA concentration in the cortex, demonstrated in some cases through magnetic resonance [25–28]. Other authors have suggested a certain GABA-ergic hypofunction in BPD. The first to suggest an alteration of GABA in mood disorders was Emrich et al. [29], based on the effectiveness of valproate that was found after administration to patients with BPD. Different authors have also described objective deficits in gabaergic transmission in the prefrontal cortex, the limbic system, and the cerebellum in individuals with schizophrenia [30–32]. It has been suggested that an imbalance in the GABA/dopamine interaction would contribute to the pathophysiology of schizophrenia [33–35]. In this sense some studies have demonstrated a modulatory capacity of the GABA on the dopaminergic system that causes changes in the HVA [36, 37]. Diverse studies have used pGABA concentration as a reflection of brain activity. Of particular interest were the studies in BPD done by Petty et al. [7, 25] that suggested the pGABA determination as a blood test of this disorder. Subsequently it was suggested that the decrease of pGABA values was associated only to a sub-group of bipolar patients [38] while other authors suggest a simultaneous alteration of the gabaergic function together with other monoaminergic systems [39].

In this context we have started an investigation of biological markers in schizophrenia and bipolar disorder, beginning with the analysis of the differences in pHVA and pGABA concentrations among normal controls, schizophrenics and bipolar I patients, in a geographic zone of relative ethnic homogeneity. We have also verified the influence of gender and age on the mentioned levels.

Technically we were fortunate with the wide spread of high-resolution liquid chromatography (HPLC) which enables many laboratories to determine neurotransmitters and their metabolites. In the method section we will provide a more detailed description of the one developed to determine pGABA, since we had not previously published the details of this technique, as was done with pHVA-determination techniques [40].

Experimental Procedure

Subjects

The sample consisted of: 104 healthy controls that were not undergoing any pharmacological treatment and that had no record of psychiatric disease; 74 bipolar patients of type I; and 50 patients with schizophrenia. Patients were selected among those admitted consecutively in two hospitals of the Basque Health Service (Zamudio and Basurto). Patients were of both sexes, between 18 and 64 years of age, and free from serious organic disease, as well as drug addiction, pregnancy or breastfeeding. The patients were diagnosed according to the diagnostic an statistical manual of mental disorders revised (DSM-IV-TR) [41] based on the data obtained by two experienced psychiatrists through structured interview [42]. The patients had a need for treatment, and they fulfilled the following requirements: for at least the previous 2 weeks none of them had received any neuroleptic medication, and for at least the past week they had taken no other psychoactive medication.

Patients were informed of the details of the study signing a written consent to take part in it. This study fulfills the requirements of the Helsinki declaration, and was approved by the ethics committee of the Basque Health Service. Controls for both sexes were chosen among members of the staff.

Blood Samples

Blood samples were taken from all participants between 8 and 8.30 a.m., after 30 min of rest and 12 h of fast. The samples were obtained in glass tubes with heparin, centrifuged for 10 min at 4,000g. After plasma separation, sodium metabisulfite was added in sufficient quantity to obtain a final concentration of 0.5 g/l plasma. The samples were stored in liquid nitrogen until their analysis.

Biochemical Assays

The pHVA concentration was assessed with HPLC and coulombimetric detection, as previously described [40].

The determination of pGABA concentration was carried out by HPLC with fluorescence detection, with excitation and emission wavelengths set at 330 and 360 nm, respectively, after pre-column derivatization by means of *o*-phthalaldehyde. The column was an ACE 5 C18HL, which is 250 × 4.6 mm with 5 µm particle size set at 28°C. The precolumn was an 5 µm C18. The mobile phase consisted of 0.1 M sodium dihydrogen phosphate (pH = 4.5) with 8% methanol and 4% acetonitrile (v/v) at a flow rate of 1 ml/min.

A GABA stock solution (1 mg/ml) was prepared in water: methanol (1/1; v/v) and stored for up to 5 days at 4°C. The working solution of the derivatization agent consisted of a mixture (2/2/1; v/v/v) of 50 mM sodium tetraborate containing 0.1 mM EDTA (pH 9.4), *o*-phthalaldehyde (5.4 mg/ml in methanol) and sodium sulfite (5 mg/ml in water). For the derivatization reaction, we used 11 µl of the derivatization agent per 40 µl of standard or plasma samples.

When required for analysis, the plasma samples were defrosted and centrifuged for 5 min at 4,000g in a refrigerated centrifuge at 5°C. Then 150 µl of plasma were deproteinized using Vivaspin 500 filters with 30,000 NMW by centrifugation at 4,000g during 30 min at 5°C. Next, 90 µl of filtered plasma were reacted with 25 µl of the derivatization agent. Samples were placed in the automatic injector; and after 5 min of reaction time at 5°C in the dark, 50 µl [of reacted sample] were injected into the HPLC system. To calculate pGABA concentration in samples, the GABA peak heights in each sample were compared with the height of a standard GABA peak.

This method was found to be adequate, with samples presenting high recovery (90.6–99.8%); the intra and inter-day precisions were good, with the variation coefficient ranging from 4.83 to 6.48%, (intra-day) and 4.45, to 6.90% (inter-day).

Statistical Analysis

The statistical analysis of the results was carried out using Statgraphics Plus software. The data distribution analysis was carried out by means of Chi-square test; and the presence of atypical values was established by the Grubbs test. When lack of normality was observed, with a presence of atypical values, a logarithmic transformation was made to solve this problem.

Plasma concentrations of HVA and GABA, as well as pHVA/pGABA quotients through the different groups, were analyzed by means of analysis of variance (ANOVA) followed by post hoc analysis with the Student's Newman Keuls test (SNK). We studied the possible influence of age and sex on the plasma concentrations of HVA and GABA in the different diagnostic groups by means of analysis of covariance. Correlations between plasma concentrations of HVA, GABA and age were made by means of a Pearson test.

Results

The sample data is shown in Table 1. In this sample there were: 104 controls (64 women and 40 men). The age range was between 18–64 years old, with an average age of 44.7 ± 10.2 years. There were 74 Type I bipolar patients, (46 women and 28 men), aged between 19 and 52 years old, with an average age of 35.0 ± 9.6; and 50 schizophrenic patients, (24 women and 26 men), their age ranging between 18 and 63, with an average age of 35.1 ± 11.3.

The pGABA concentrations among controls, and in bipolar and schizophrenic patients, presented a normal distribution. This was not so in the case of pHVA levels, where logarithmic transformation was required to treat the data. We also observed that the dispersion of the data was greater among schizophrenics than it was among controls and bipolar patients. Table 2 lists pHVA and pGABA and the pHVA/pGABA quotient concentrations in each experimental group. We observed a significantly greater concentration of pHVA in schizophrenic rather than in the bipolar patients, (SNK $P < 0.001$). When age was included in the model as a covariate, differences in pHVA concentrations remained between schizophrenics and bipolar patients (SNK $P < 0.05$). Influence of gender is not significant and did not alter these results.

Table 1 Demographic, clinical and neurochemical data in the bipolar and schizophrenic patients and controls

	N			Age (years)		
	Total	Women	Men	Total	Women	Men
Bipolar patients	74	46	28	35.0 ± 9.6	36.6 ± 10.2	32.2 ± 7.9
Schizophrenics	50	24	26	35.1 ± 11.3	35.9 ± 11.4	34.4 ± 11.4
Controls	104	64	40	44.7 ± 10.2	43.0 ± 9.5	47.4 ± 10.9
Total	228	134	94	39.2 ± 11.2	39.6 ± 10.5	39.5 ± 12.4

Data are presented as mean ± SD

N Number of individuals

Table 2 Concentrations of plasma homovanillic acid (pHVA), gamma-aminobutyric acid (pGABA) and their ratio (pHVA/pGABA) from bipolar and schizophrenic patients and controls

	pHVA (ng/ml)	pGABA (ng/ml)	pHVA/pGABA	*N*
Bipolar patients	12.90 ± 5.12	10.80 ± 2.53	1.27 ± 0.62	74
Schizophrenics	14.40 ± 6.97*	11.28 ± 3.21	1.54 ± 1.00***	50
Controls	14.1 ± 5.74	13.40 ± 2.75**	1.11 ± 0.26	104

Data are presented as mean ± SD

N Number of individuals

pHVA: ANOVA: $F = 3.47$, $P = 0.033$, d*f* (2,225); * Significant differences between schizophrenic and bipolar patients: (SNK $P < 0.05$)

pGABA: ANOVA: $F = 21.42$, $P < 0.001$, d*f* (2,224); ** Significant differences in controls compared to schizophrenics and bipolar patients (SNK $P < 0.05$)

pHVA/pGABA: ANOVA: $F = 6.74$, $P = 0.001$, d*f* (2,224); *** Significant differences in schizophrenic patients compared to the group of bipolar patients and controls (SNK $P < 0.05$)

We found significantly lower levels of pGABA in the schizophrenic and bipolar groups than in the controls (SNK $P < 0.001$) Effects for the diagnostic groups remained significant after controlling for gender and age.

The pHVA/pGABA quotient is significantly higher in the schizophrenic patients compared to the group of bipolar patients and controls (SNK $P < 0.001$). When we analyzed the data considering the influence of age, the above mentioned differences remained, and differences emerged between bipolars and controls, being the pHVA/pGABA quotient in bipolar patients greater than in controls (SNK $P < 0.05$). The influence of gender was non significant and did not alter those results.

The pHVA concentration correlated significantly and positively with age only among controls ($r = 0.364$; $P < 0.001$). The age-pHVA correlation for controls was not significantly influenced by the presence of a greater number of older people in the group. The correlation remained significant ($P = 0.009$) when including in the control group only people aged between 18 and 53.

Gender did not significantly influence pHVA and pGABA concentrations in any of the groups of our sample. There was no correlation between the values of pHVA and pGABA, either among controls or among patients.

Discussion

There are more women than men, both among controls and among patients with bipolar disorder, (61 and 62%, respectively). In the schizophrenic group the number of individuals of both genders is balanced. This fact does not seem to affect results, since in our sample gender does not influence the pGABA and pHVA concentrations. The age is higher among controls than it was among schizophrenic and bipolar patients, which influenced the results slightly. Within each group there is no age difference between men and women. It seems that the absence of a significant relation between pHVA concentration and the patient's age has to do with either the previous medication or the pathological process, or both factors simultaneously.

The frequency of abnormal distributions found in the pHVA concentrations in patients, and the high standard deviations of values in schizophrenic patients, (compared with the ones found in normal controls and in patients with bipolar disorder), must be noted (see Table 2); this could be due to both previous treatments and the heterogeneity of the sample, alluded to in our introduction,. This heterogeneity can also be related to the so-called comorbidity, although this may not serve as a clarifying criterion. Using

the current criteria for diagnoses (i.e. DSM-IV), it is perfectly possible that comorbidity simply responds to the fact that sometimes inevitably many patients receive several diagnoses, though their different symptoms share the same etiology [43]. Indeed, a rational use of the parameters measured would facilitate an objective subdivision of patients. Consequently, we have recently found a basis on which to build a division between bipolar patients with congruent or incongruent psychotic symptoms [23].

On the other hand, the results regarding pGABA concentrations in different groups are coherent with the observation of patients with bipolar disorder by Berrettini et al. [44] and Petty et al. [10] and our findings differ from those found by the same authors among schizophrenics: observing no differences when compared with controls [25, 38]. Nevertheless, most post-mortem studies of schizophrenic patients have revealed GABA reductions in different brain areas [45–48]. The fact that variations can be found in the pGABA concentration in both patient types supports the idea of the gabaergic system being involved in the schizophrenic and bipolar disorder, perhaps through an abnormal interaction between dopamine and GABA [10, 29, 30, 32, 34, 39, 49, 50].

Regarding the interaction between dopamine and GABA, we consider the pHVA/pGABA quotient to be more informative of the balance between neurotransmission systems than our isolated values. It is possible that in future longitudinal studies, the variations in pHVA/pGABA quotient could reflect the adaptation to pharmacological treatment and also demonstrate whether the quotient contributes to lessen the influence of uncontrolled individual deviations. The significant elevation of pHVA/pGABA quotients in the patients as opposed to the controls, supports the idea of a global inhibiting modulation of GABA in dopaminergic activity [34]. It would be interesting, given the abnormal distributions and high standard deviations of pHVA, to study a greater number of patients to see if there exist sub-groups which concentrate increased or decrease values for pHVA/pGABA quotients. For example, with patients as with non ill relatives, it would be of interest to trace the influence of family history or the role of inheritance in clinical subgroups. We considered this high quotient to have a potential value for diagnosis, or as a marker, such as in studies on how mutations of some genes (i.e., neuroligine and neurexine) [1], can alter the balance between exciting and inhibiting transmission, or in studies on the relation of certain genetic polymorphisms with certain personality features [51].

It is possible that some genetic variants which are common to bipolar and schizophrenic disorders, although they may not always coincide, could contribute to increasing the ratio of dopaminergic/gabaergic activity throughout the whole spectrum: bipolar, schizo-affective, and schizophrenia. Recent findings contribute to the idea of shared genetic factors and support the existence of an overlap in the gene of susceptibility for schizophrenia and bipolar disorder [43]. The largest family study ever published on schizophrenia and bipolar disorder [52] reported that first degree relatives of patients with schizophrenia or bipolar disorder have an increased risk of suffering from both disorders; and that this effect is mainly due to genetic factors, concluding that both disorders share a common genetic cause.

From this point of view it is difficult to explain the difference we have found in the pHVA concentration between bipolar and schizophrenic patients. It may be that our study is underpowered to explore the question of diagnostic overlap, or that it is limited by a different time of washout or by different treatments derived from diagnosis. But, ultimately, the greatest limitation is our ignorance of the ethiopathogeny of both disorders (or if they are one, two or one hundred different disorders). Due to the intervention of multiple genes and to the different intensity of participation of each gene in each individual, together with the phenomenological approach to categorial diagnosis, it is not surprising that the results of a large study [52] show an appearance of homogeneity in what is really a mixture of many illness. It is conceivable that there is no unitary basis for both disorders and that each entity is a heterogeneous one resulting from the numerous interactions between multiple genes and between the environment and of variable intensity.

Future research is necessary to include the variation of the parameters studied here during treatment, and their relation with the presence of specific polymorphisms. This would link their relation with a proneness to suffer from certain symptoms independently of categorial diagnosis.

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