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Research Report

Cerebrospinal fluid GABA levels in chronic migraine with and without depression

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ABSTRACT

Psychiatric comorbidity is one of the key elements in chronic migraine (CM) management. Depression is particularly common in these patients, occurring in up to 85%. Preclinical studies have suggested that gamma-aminobutyric acid (GABA) levels may be decreased in animal models of depression. Also, clinical studies have reported low level in mood disorder patients for both plasma and cerebrospinal fluid (CSF) GABA. We hypothesized that low GABA levels in the brain might be related to the depression associated with CM. We studied 14 chronic migraine patients, with or without depression, compared to age-and sex-matched controls. CSF GABA levels were measured by HPLC. CSF GABA levels showed significant lower levels in depressed patients than those without depression. No difference was found when comparing patients versus controls. A GABA deficiency may be the underlying mechanism of depression in CM. Hence, preventive therapies modulating GABA neurotransmission could be used in CM associated with depression.

1. Introduction

Numerous biochemical studies on migraine have failed to identify the underlying mechanisms responsible for this syndrome. Gamma-aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the brain. In regions, such as the cerebral cortex, hippocampus, thalamus, basal ganglia, cerebellum, hypothalamus, and brainstem, this amino acid is released by about one-third of all synapses. This means that it is in larger concentration than other neurotransmitters in the same regions (Brambilla et al., 2003). Noradrenergic, dopaminergic, serotonergic, and glutamatergic neurons are all under GABAergic inhibitory control. GABA is synthesized from its precursor glutamate through the action of glutamate decarboxylase (GAD) and exerts its effects by acting on two brain receptors named $GABA_A$ and $GABA_B$ (Shian and Yathanm, 1998).

The possible role of GABA in the pathophysiology of migraine has been based in its inhibitory function in most of brain synapses, including its involvement in vasodilatation (Anwar and Mason, 1982; Alborch et al., 1984; Fergus and Lee, 1997; Barbelivien et al., 1999). In this sense, Welch et al. (1975) found that GABA levels in cerebrospinal fluid (CSF) of patients during migraine attack were higher when compared to those found during a headache-free period and Kowa et al. (1992) reported higher GABA levels in blood platelet of patients suffering from tension headache. These findings might be related to a GABA increase in response to pain more than its direct participation in the physiopathological process underlying migraine.

CM is a common disorder affecting 2–3% of the general population and it is one of the most debilitating and difficult disorders to treat in headache centers (Kavuk et al., 2003). Psychiatric comorbidity is one of the key elements in chronic

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migraine (CM) management. Depression is particularly common in these patients, some degree of depression (including mild cases) was found in up to 85%; furthermore, severe depression was found in 25% of CM patients (Mercante et al., 2005). GABA neurotransmission has been linked to the pathophysiology of depression in experimental, neuroimaging and clinical studies. Furthermore, decreased GABA levels in CSF and serum have been reported in depression (Brambilla et al., 2003; Shian and Yathanm, 1998; Petty, 1995; Lloyd et al., 1987a, 1989; Tunnicliff and Malatynska, 2003; Petty and Sherman, 1981, 1984; Petty and Schlesser, 1981; Petty et al., 1990; Emrich et al., 1980; Gold et al., 1980; Kasa et al., 1982; Post et al., 1980; Petty, 1994). Despite the relevance of depression in chronic migraine, little is known about their mechanisms. We hypothesized that GABA levels might be related to the mechanisms of depression in CM patients. Accordingly, we have measured the GABA levels in the cerebrospinal fluid of CM patients as well as in controls subjects and its relationship with depression is discussed.

2. Results

All CSF studied presented normal levels of protein, glucose, lactate, as well as the cell count.

CSF GABA levels in CM patients was not statistically different from that observed in controls. When analyzed by the occurrence of depression as comorbidity, it was possible to verify that the GABA level in CM plus depression patients (7.29 ± 1.44 μmol/l) was lower than that observed in patients with CM without depression (8.3 ± 1.12 μmol/l) ($P < 0.04$) and in controls (8.46 ± 1.93 μmol/l) (Fig. 1).

3. Discussion

Depression is the most frequent psychiatric condition associated with migraine. Moderate or severe depression has been reported in 58.7% of the patients with it (Mercante et al., 2005).

Our study shows decreased GABA levels in the CSF of patients with CM plus depression when compared to those patients without psychiatry symptoms and controls subjects. A limitation of our study was the use of the Beck Depression Inventory rather than a structured interview; however, a good correlation has been established between Beck scores and structured interviews (Beck et al., 1961; American Psychiatric Association, 1994). Several studies have showed abnormal GABA levels in depression, including preclinical and clinical data (Brambilla et al., 2003; Shian and Yathanm, 1998; Petty, 1995; Lloyd et al., 1989; Tunnicliff and Malatynska, 2003; Lloyd et al., 1987a).

GABA in GABAergic terminals is formed from glutamate in an enzymatic reaction, using pyridoxal phosphate as cofactor, mediated by glutamate acid decarboxylase (GAD). After being released into the synapses, GABA is inactivated by reuptake into presynaptic terminals or into glial cells mediated by GABA transporter (GATs). At the present time, four complementary DNAs encoding high homologous GATs proteins have been cloned (GAT-1, GAT-2, GAT-3, and BGT-1). GAD is localized only in GABAergic presynaptic terminals, lacking in glial cells. Two forms have been discovered so far (GAD_{65} GAD_{67}).

GABAergic receptors are composed by two main types with different distribution on the neuronal surface, $GABA_A$, and $GABA_B$ receptors. $GABA_A$ receptors are ionotropic and mostly postsynaptic receptors, mainly located at the apical dendrite of the neurons. It causes the fast inhibitory postsynaptic potential (IPSP). $GABA_B$ receptors are mainly located at presynaptic terminal soma and mediate the slow IPSP (Brambilla et al., 2003).

When inescapable shocks are administered to animals, they demonstrate subsequent inability to perform a simple escape task in shuttle box (Petty, 1995). One call learned helplessness this stress-induced depressive behavior. Petty and Sherman (1981) demonstrated that GABA injection into frontal neocortex and hippocampus reversed the learned helplessness reaction. Also, they reported two things: (1) injection of bicuculline, a $GABA_A$ receptors antagonist, into hippocampus produced learned helplessness in naive non-stressed rats; and (2) a chronic administration of tricyclic antidepressants normalized both, the hippocampal GABA

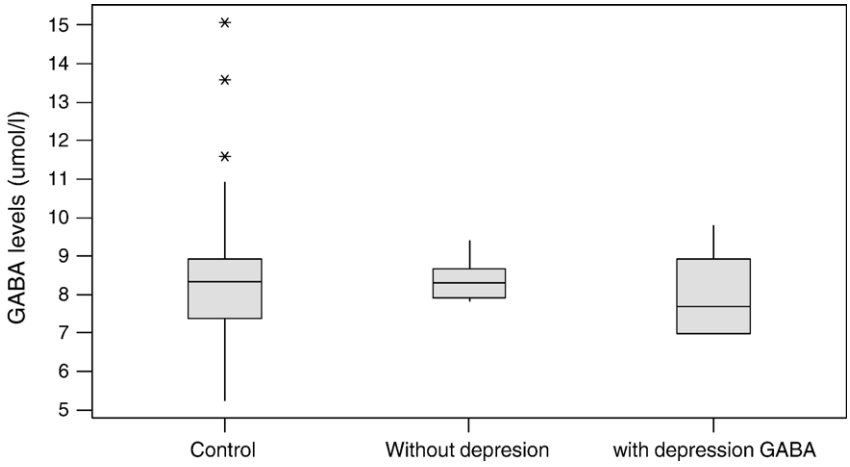

Fig. 1 – Cerebrospinal fluid glutamate levels in chronic migraine patients with and without depression and controls.

release and the helpless behavior (Sherman and Petty, 1980). In another preclinical study, rats that have had their olfactory bulbs removed showed increase in locomotor activities, deficits in memory, changes in food-motivated behavior, and a pervasive deficit in passive-avoidance learning (Kelly et al., 1997). Following olfactory bulbectomy, GABA turnover was reported to increase in rat amygdaloid cortex (Jancsar and Leonard, 1984). Furthermore, the binding on $GABA_B$ receptor in frontal cortex, but not in other brain regions, has been found to be decreased about 50% in this model. However, the binding on $GABA_A$ receptor increased in frontal cortex and, transiently, in the hippocampus of this rats (Lloyd and Pichat, 1986; Dennis et al., 1993). On the other hand, desipramine reversed the behavior deficit in rats with olfactory bulbectomy, increasing the cortex $GABA_B$ receptor density. It has also been showed that baclofen, progabide, and fengabide reverse the behavioral deficit in this model (Joly et al., 1987; Lloyd et al., 1987b; Drugan et al., 1989).

A role of GABA in mood disorders was first postulated by Emrich et al. (1980), based on the clinical observation that valproate, a GABA agonist, which was effective in the treatment of bipolar affective disorder.

The GABA level on CSF GABA originates from brain and may reflect the GABAergic brain activity (Grove et al., 1982; Loscher, 1982). Lower CSF GABA levels have been found in unipolar (Gold et al., 1980; Gener et al., 1984) and bipolar patients when compared to control values (Berrettini et al., 1983). However, other studies showed no abnormalities in GABA CSF levels in unipolar disorder (Post et al., 1980) and, especially, in bipolar patients (Gener et al., 1984; Post et al., 1980; Berrettini et al., 1986). Discrepancies between positive and negative studies may be in part explained by methodological differences, such as the aliquot of CSF examined and the subject characteristics (i.e., age, gender, mood) (Post et al., 1980; Berrettini et al., 1986).

There is some evidence to suggest that plasma levels reflect brain GABA activities (Petty, 1994). For example, GABA levels in plasma have been reported to be almost identical to levels in CSF, suggesting that there is no active gradient between these two compartments. Furthermore, after pharmacological manipulations GABA levels change in similar proportion (Ferkany et al., 1978; Loscher and Frey, 1982). Some studies have shown that depressed patients have lower plasma GABA levels, when compared with matched normal controls (Petty and Schlesser, 1981; Petty and Sherman, 1984; Petty et al., 1990). Moreover, Petty et al. (1995) reported that, in patients with major depression, plasma GABA levels were stable for 4-year follow-up and did not change with clinical improvement. This suggests that low plasma may be a trait marker for the depressive illness. In addition, mean levels of plasma GABA were reported to be significantly lower in both manic and depressive phases of bipolar patients, when compared to healthy individuals (Petty et al., 1993).

Perry et al. (1977) studied activities of GAD in brain regions of patients with depression and they reported that GAD activities were significantly decreased in frontal cortex, occipital cortex, and basal ganglia of depressed patients when compared to controls values. $GABA_A$ receptor binding sites have been found to be abnormally increased in frontal cortex of depressed suicide victims (Cheetham et al., 1988), suggesting lowered GABAergic activity in those patients. However, no significant differences have been found in several brain areas between suicide victims and nonpsychiatric controls for $GABA_A$ and $GABA_B$ receptor binding sites, GAD activity, and GABA concentration.

A recent SPECT study reported abnormally decreased $GABA_A$ receptor density in the prefrontal cortex of mood disorder patients, mainly bipolar, with or without akinetic catatonia, a psychomotor syndrome that can be seen in mood disorders and responsive to lorazepam (Northoff et al., 1999).

Welch et al. (1975) and Kowa et al. (1992) reported that GABA levels in CSF and platelets were increased in patients suffering of migraine and tensional headache as a possible compensatory response to pain. We hypothesize that there were no differences between controls and patients with CM without psychiatry symptoms because there might be a response promoting a GABA increase in these individuals. This response mechanism is supposedly impaired in patients with CM and depression, justifying why low GABA levels were observed only in those depressed patients, and not in nondepressed patients, where the compensatory GABA response to pain is normal (Brambilla et al., 2003; Shian and Yathanm, 1998; Petty, 1994, 1995; Petty and Schlesser, 1981; Petty and Sherman, 1981, 1984; Petty et al., 1990; Lloyd et al., 1989; Tunnicliff and Malatynska, 2003; Lloyd et al., 1987a; Emrich et al., 1980; Gold et al., 1980; Kasa et al., 1982; Post et al., 1980).

Current biochemical hypotheses of mood disorders implicate biogenic amine neurotransmitters such as serotonin and norepinephrine. This happens in either the pathophysiology of depression and mania or in the mechanism of action of mood-altering treatments. However, most antidepressants and mood stabilizers in clinical use affect a number of neurotransmitter receptors, in addition to those related to norepinephrine and serotonin. We consider that other neurotransmitter systems, such as the GABA system, may be deranged in mood disorders alone, but also in mood disorders present in chronic migraine. Then, antidepressants and mood stabilizers, or eventually other medications with GABA activity, may be important in the management of important in the management of psychiatric comorbidity in chronic migraine. Future studies are still necessary for a better understanding of the putative role of the GABAergic neurotransmission in migraine headaches and their psychiatric comorbidity disorders.

4. Experimental procedures

Fourteen patients (3 male, 11 female) were diagnosed with chronic migraine according to Silberstein et al. and the International Headache Society (IHS-2004) criteria (Silberstein et al., 1996; Headache Classification Subcommittee of the International Headache Society, 2004). Patients met both IHS and Silberstein's criteria. Patients underwent a lumbar puncture in order to rule idiopathic intracranial hypertension, which is present in 5–14% of chronic daily headache series (Mathew et al., 1996; Quattrone et al., 2001). Six patients were included in the group of patients presenting chronic migraine and depression. The presence of depression was considered when the Beck Depression

Inventory (BDI II) was higher than 16. A good correlation between the BDI II score (cutoff level of 16) and the DSM IV diagnostic criteria for major depression is achieved (Beck et al., 1961; American Psychiatric Association, 1994). The remaining eight patients presented only chronic migraine.

Controlled CSF specimens were also obtained from 14 age- and sex-matched subjects who underwent lumbar puncture for others diagnostic purposes. Their CSF and blood tests were normal. When necessary, instrumental investigations including neuroimaging also excluded CNS diseases (multiple sclerosis, vasculitis, and other autoimmune diseases affecting the CNS) or systemic diseases (diabetes, renal or hepatic dysfunction, inflammatory diseases). Neurodegenerative diseases, mood, and anxiety disorders were also excluded.

Three different groups were then analyzed: (1) CM with depression, (2) CM without depression, and (3) controls.

The protocol was approved by the local Ethics Committee and all patients gave written consent to these study. The subjects' consent was obtained according to the Declaration of Helsinki. All patients were in pain at the time of lumbar puncture.

4.1. *CSF analysis*

Sodium phosphate dibasic (Na_2HPO_4), methanol (HPLC grade), trichloroacetic, and sodium bicarbonate were acquired from Merck. Sodium tetraborate, beta-mercaptoethanol (BME), phosphoric acid (85%, HPLC grade), o-phthaldialdehyde (OPA), L-aspartic acid, L-glutamic acid, glycine, taurine, and γ-aminobutyric acid (GABA) were purchase from Sigma-Aldrich.

4.2. *Chromatography*

The Waters chromatography system consisted of the Model 600 E multisolvent pump, a 717 plus auto-sampler and 2475 multifluorescence detector (excitation 330 nm, emission 450 nm). The CSF samples were deproteinized with 10% trichloroacetic acid (1:0.2 v/v). The resulting mixture was kept at 0 °C for 15 min and then centrifuged at 3000 × *g* for 10 min at 4 °C. Supernatant (100 μl) was added to 400 μl of 0.2 M sodium bicarbonate. Amino acid determination was performed using a precolumn derivatization procedure. The reagent OPA/BME was prepared 24 h prior to use and the derivatization procedure performed by the 717 auto-sampler, just before injection. OPA (150 μl) was transferred to the sample vial. After mixing, 20 μl was injected onto a reversed phase Nova-Pak C18 (3.9 × 150 mm, 4 mm) column (Waters) equilibrated at 25 °C with mobile phase A (0.05 M sodium phosphate buffer pH 5.5/15% methanol) at a flow rate of 1 ml/min. The mobile phase B consisted of sodium phosphate pH 5.5/80% methanol. The GABA was eluted after the establishment of a linear gradient as previously described by Cavalheiro et al. (1994). The elution program consisted of 20 min of elution with only the mobile phase A and a gradual change to mobile phase B during a period of 40 min, followed by 20 min with pure mobile phase B. After this, the column was re-equilibrated with the mobile phase A during 10 min before the next injection. Standard solutions containing glutamate were employed to establish calibration curves (correlation coefficients of 0.99 or better in all cases).

4.3. *Statistical analysis*

The values in μmol/l were expressed as mean ± SD. One-way within-subjects ANOVA was carried out to compare GABA levels from CSF. A Student's *t* test was used to compare groups. Five percent for two-sided tests was chosen as a minimum level of statistical significance.

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