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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

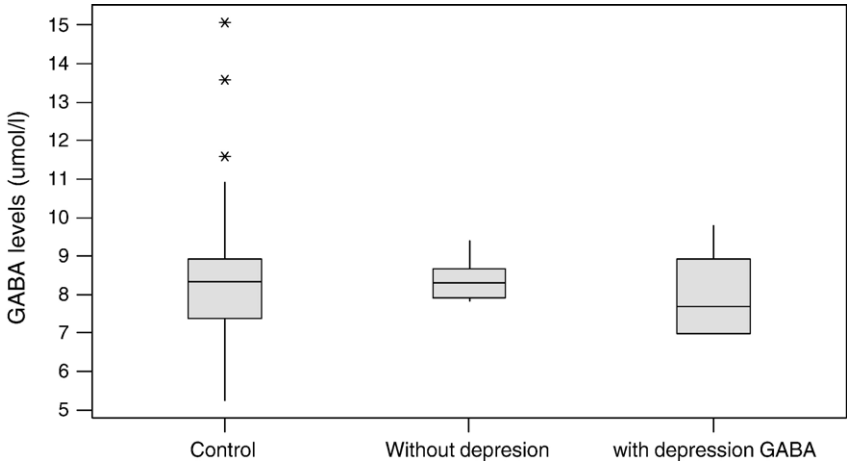

Fig. 1 – Cerebrospinal fluid glutamate levels in chronic migraine patients with and without depression and controls.