Measuring Human Brain GABA In Vivo

Effects of GABA-Transaminase Inhibition with Vigabatrin

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Abstract

Gamma-aminobutyric acid (GABA) plays a pivotal role in suppressing the origin and spread of seizure activity. Low occipital lobe GABA was associated with poor seizure control in patients with complex partial seizures. Vigabatrin irreversibly inhibits GABA-transaminase, raising brain and cerebrospinal fluid (CSF) GABA concentrations. The effect of vigabatrin on occipital lobe GABA concentrations was measured by in vivo nuclear magnetic-resonance spectroscopy. Using a single oral dose of vigabatrin, the rate of GABA synthesis in human brain was estimated at 17% of the Krebs cycle rate. As the daily dose of vigabatrin was increased to up to 3 g, the fractional elevation of brain GABA was similar to CSF increase. Doubling the daily dose from 3 to 6 g failed to increase brain GABA further. Increased GABA concentrations appear to reduce GABA synthesis in humans as it does in animals. With traditional antiepileptic drugs, remission of the seizure disorder was associated with normal GABA levels. With vigabatrin, elevated CSF and brain GABA was associated with improved seizure control. Vigabatrin enhances the vesicular and nonvesicular release of GABA. The release of GABA during seizures may be mediated in part by transporter reversal that may serve as an important protective mechanism. During a seizure, this mechanism may be critical in stopping the seizure or preventing its spread.

Index Entries: Human; brain; epilepsy; gamma-aminobutyric acid; vigabatrin; antiepileptic drugs; $^1$H nuclear magnetic resonance spectroscopy; glutamic acid decarboxylase; GABA-transaminase; GABA-transporter.

Introduction

Gamma-aminobutyric acid has had a central role in neural control theory since it was first discovered in 1950 (Roberts and Frankel, 1950; Roberts, 1986, 1988). It is a major inhibitory neurotransmitter in mammalian brain and in human cortex (Roberts, 1986; Lloyd et al., 1986). GABA may serve as the primary inhibitory neurotransmitter at 25–50% of synapses in the mam-
malian brain (Lloyd et al., 1986; Kocsis and Mattson, 1996). Changes in GABA metabolism may play an important role in the origin and spread of seizure activity. The level of GABA in synaptic terminals and in the extracellular fluid depends on the functioning of a metabolic cycle between neurons and glia. The effectiveness of the class of anti-epileptic drugs that target GABA metabolism (e.g., vigabatrin, gabapentin, valproate) hinges on the elevation of GABA concentration.

GABA is formed from the alpha-decarboxylation of glutamate by glutamic acid decarboxylase (GAD) and is metabolized to succinate by the sequential actions of GABA-transaminase (GABA-T) and succinic semi-aldehyde dehydrogenase (SSADH). There are several ways of increasing GABA activity in the brain. GABA agonists, e.g., progabide, diazepam, and phenobarbital, directly increase inhibitory chloride conductances or upregulate the effect of synaptically released GABA on the GABA-A receptor. GABA transporter blockers, e.g., tiagabine, prolong the action of GABA in the synaptic cleft by inhibiting uptake. Stimulating GABA synthesis and release, e.g., valproate, gabapentin, would increase synaptic GABA during neuronal activation. Slowing degradation of GABA, e.g., vigabatrin, valproate, by inhibiting GABA-T or SSADH increases intracellular and extracellular GABA concentrations. Recent studies in animal models and human patients show that multiple feedback mechanisms control both GABA concentration and inhibitory activity.

**GABA Synthesis Is Regulated by Specific Modulators**

The activity of GAD is believed to be primarily responsible for regulating the steady-state concentration of GABA in vivo through the pyridoxal-5P-dependent interconversion of holo- (active) and apoenzyme (inactive) forms (Bernasconi et al., 1984; Martin, 1987). The activation of GAD (to holoenzyme) is stimulated by inorganic phosphate (P_i) and inhibited (increased level of apoenzyme) by ATP, GABA, glutamate, and aspartate (Martin, 1987). GAD is comprised of two major isoforms (65-kDa and 67-kD proteins), which are the products of two different genes (Martin and Rimvall, 1993; Erlander and Tobin, 1991) GAD_{65} also comprises the major pool of apoenzyme and may be involved in short-term changes in GABA synthesis flux and GABAergic function (Martin and Rimvall, 1993).

**Cellular Compartmentation Is Important in GABA Metabolism**

The metabolism of GABA associated with nerve terminals has been linked to a substrate cycle between neurons and astrocytes involving glutamate, GABA, and glutamine (Shank et al., 1993; Schousboe et al., 1992; Sonnewald et al., 1993). In this cycle, nerve-terminal GABA is synthesized from glutamate, enters the extracellular fluid by neurotransmitter release, from which it is either recycled into the nerve terminal or taken up by astrocytes (Fig. 1). In the astrocyte, GABA is broken down by GABA-T and resynthesized into glutamate through the tricarboxylic acid cycle (TCA cycle) of mitochondria. Astrocytic glutamate is converted into glutamine that is taken up by nerve terminals. In the nerve terminal, the released glutamine is hydrolyzed to glutamate by glutaminase (PAG). The flow of carbon between nerve terminal and glia, i.e., the glutamate-GABA-glutamine cycle, maintains nerve-terminal GABA transmitter stores (Schousboe et al., 1992; Sonnewald et al., 1993). Evidence based on selective lesioning, immunohistochemical localization of enzymes of GABA and glutamine metabolism, and isotopic labeling studies support the importance of this cycle (Shank et al., 1993, Schousboe et al., 1992; Sonnewald et al., 1993). GAD is highly enriched in nerve terminals. GABA-T, involved in the degradation of GABA, is enriched in nonsynaptic mitochondria associated with glia (Sonnewald et al., 1993; Sellstrom et al., 1975). Astrocytes serve as the site of glutamine synthesis because of the preferential localization of glutamine synthetase (GS) (Wiesinger, 1995; Ward et al., 1983;