PHARMACOLOGICAL PROFILE OF THE GABA-TRANSAMINASE INHIBITOR VIGABATRIN

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ABSTRACT

In the central nervous system, several lines of evidence suggest that the well-characterized inhibitory neurotransmitter gamma-aminobutyric acid (GABA) is involved directly and/or indirectly in the pathogenesis of many neuropsychiatric disorders such as Alzheimer's disease, epilepsy, depression, schizophrenia, anxiety and some other disorders. Accordingly, deficiency in the GABA-ergic system activity in the brain should produce convulsion. Consequently, manipulation of the GABA-ergic activity seems to represent a possible treatment for epilepsy which has extensively been explored. Vigabatrin, an irreversible inhibitor of the catabolic enzyme of GABA (GABA-transaminase), is accepted as adjunct therapy of refractory partial seizures and infantile spasms. Although vigabatrin was demonstrated to be effective, its use is limited by the risk of retinopathy and associated peripheral visual field defects. Thus, this review highlights and assesses the accessible literature of the fundamental and clinical aspects of the GABA-transaminase inhibitor vigabatrin.

KEYWORDS: Vigabatrin, GABA-transaminase, GABA, Epilepsy, anti-epileptic drug.

INTRODUCTION

Over the last decades, there is a great deal of interest in the inhibitory amino acid neurotransmitter, gamma-aminobutyric acid (GABA), and its relation to neurologic diseases and psychiatric disorders. Thus, various reports indicated that GABA is involved directly and indirectly in the pathogenesis of certain neuropsychiatric disorders such as Huntington's chorea, Parkinsonism, Alzheimer's disease, tardive dyskinesia, epilepsy, schizophrenia, depression, anxiety and some other behavioral disorders.\[1, 2\]
The GABA system

After the first report of the presence of GABA in the brain in 1950, several basic studies on the GABA system have been published (see 3 for historical recount). Over these years, GABA was well-established and well-accepted as the most widely distributed inhibitory neurotransmitter in the CNS. GABA is found in high levels in the brain and spinal cord; however, it is absent or present only in trace levels in the peripheral nerve tissue or in any other peripheral tissue such as liver, spleen, heart and in the blood.\textsuperscript{[4]} In the brain, GABA is synthesized in the presynaptic nerve terminals by decarboxylation of glutamic acid (GA), the process being catalyzed by the enzyme glutamic acid decarboxylase (GAD) and released into the synaptic cleft where it activates the postsynaptic GABA receptors. Then, GABA is taken up by presynaptic nerve terminals and glial cells. Degradation of GABA is catabolized by the enzyme GABA-transaminase (GABA-T) into glutamic acid (GA) and succinic semialdehyde using the coenzyme pyridoxal phosphate.\textsuperscript{[4,5]} GABA interacts with different receptors namely GABA\textsubscript{A}, GABA\textsubscript{B} and GABA\textsubscript{C} of which the post-synaptic GABA\textsubscript{A} receptors are the most significant in controlling the inhibitory function by chloride channels, producing in hyperpolarization of the nerve membrane potential. GABA is also taken up by pre-synaptic nerve terminals and glia and during uptake it is metabolized by GABA-T.\textsuperscript{[2,4]} Cloning of the GABA receptors showing that the GABA\textsubscript{B} receptor functions as a heterodimer with GABA\textsubscript{B1b}/GABA\textsubscript{B2} mediating postsynaptic inhibition and GABA\textsubscript{B1a}/GABA\textsubscript{B2} mediating presynaptic inhibition.

Pharmacology of vigabatrin

In several studies, inhibition of GABA-T activity by some potent and relatively-specific compounds such as amino-oxyacetic acid, ethanolamine-O-sulphate, gamma-acetylenic acid, 4-hydroxybenzaldehyde and 3-chloro-1-(4-hydroxyphenyl)propan-1-one and gamma-vinyl GABA (vigabatrin, GVG) has previously been found to increase brain GABA concentrations.\textsuperscript{[1,4,6]} Among these inhibitors, vigabatrin is one of the most significantly studied GABA-T inhibitor in animal and man. Thus, in the rat brain, vigabatrin was found to produce several increases in GABA levels by ten times.\textsuperscript{[4]} Since these compounds (GABA-T inhibitors) were found to inhibit other enzymes and have a less effect on the activity of brain GABA-T, thus, the clinical use of these agents is limited\textsuperscript{[7,8]} with exception of vigabatrin.\textsuperscript{[8]} However, data from reports of short- and long-term use of specific inhibitors of GABA-T have shown that only 20% inhibition of this enzyme is sufficient to cause an obvious rise in the brain GABA levels.\textsuperscript{[9]} Thus, under these conditions, GABA accumulates in nerve endings
and non-synaptosomal compartments (glial cells). It should also be mentioned that even at the highest dose of GABA-T inhibitor, a residual activity of 30% remained in the brain but completely inhibited the blood platelet enzyme.\cite{9,10} This is presumably, because the increase in plasma GABA inhibitor is extremely rapid that GABA-T is inhibited before GABA levels begin to rise appreciably.\cite{10} Biochemically, vigabatrin is a selective catalytic irreversible suicide inhibitor of the enzyme GABA-T without a change in the other neurotransmitter systems.\cite{4,11} Since vigabatrin is a structural analogue of GABA, the enzyme accepts this agent as a substrate. It is converted into a reactive intermediate which binds covalently to the active site of the enzyme, resulting in irreversible inhibition.\cite{4,8} Vigabatrin increased GABA levels in all parts of the rat brain with a dose-dependent manner.\cite{8}

**Therapeutic use of vigabatrin**

Historically, vigabatrin was developed in the 1980s. It (gamma-amino-hex-5-enoic, gamma-vinyl GABA, GVG) is the first rationally designed anti-epileptic drug that is a potent anti-convulsant in different animal models of epilepsy and an anti-epileptic drug in man.\cite{8,12,13} Although in UK vigabatrin was approved for therapy in 1989, the authorized use of vigabatrin in the US by FDA was delayed. It was delayed in 1983 because the animal trials produced intrameylinic edema but the effects have not been obvious in clinical trials so vigabatrin design continued. In 1997, the clinical trials have temporarily been suspended because it was linked to peripheral visual field defects\cite{14} (see also below). However, vigabatrin was more and more clinically used in the treatment of epilepsy in patients with a resistance to the classic anti-epileptic drugs, especially in treatment of complex partial epilepsy.\cite{13,15} In 1994, it was found that vigabatrin decreased seizures by 50-100% in 85% of the children with Lennox-Gastaut syndrome who had bad respond to valproate.\cite{16} In 2003, vigabatrin is approved, in Mexico, for the treatment of epilepsy which cannot be well controlled by the conventional therapy (adjunctive or monotherapy) or in newly diagnosed patients who have not used other drugs (monotherapy). In Canada, vigabatrin is approved for use as an adjunctive therapy with other anti-epileptic drugs in treatment of patients who are resistant to epilepsy, complex partial epilepsy, secondary generalized epilepsy, as well as for monotherapy use in infantile spasms. It should also be mentioned that vigabatrin is also indicated for monotherapy use in secondarily generalized tonic-clonic epilepsy, partial epilepsy and in infantile spasms. In 2009, FDA had decided two approvals for vigabatrin. It is indicated as monotherapy for pediatric patients one month to two years of age with infantile spasms for whom the potential benefits outweigh the potential risk of vision loss, and as
adjunctive (add-on) therapy for adult patients with refractory complex partial seizures who have poorly responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss. In a recent study by Nielsen and others\(^{17}\), vigabatrin was studied in different doses of 1, 3 and 6 gm/day in patients with refractory partial seizures. The relationship between vigabatrin dosage and daily seizure rate for adults and children with refractory complex partial seizures as well as to identify impact seizure frequency were investigated. In this study, age had no impact on vigabatrin drug effects after dosage was normalized for body weight differences. Total normalized vigabatrin dosages of 1, 3 and 6 gm/day were predicted to reduce seizure rates 23.2, 45.6 and 48.5% respectively.\(^{17}\) The anticonvulsant efficacy of vigabatrin for treatment of infantile spasms as well as for adjunctive use in the treatment of refractory complex partial epilepsy was reviewed under single-blind placebo-controlled conditions, including a long-term follow-up. In agreement with results from adult studies, the response of vigabatrin was better in partial seizures compared to generalized seizures.

A number of clinical studies has shown that vigabatrin has a reliable anticonvulsant effect in double-blind, placebo-controlled trials of patients with chronic drug-resistant epilepsy but to be used with care in patients with severe epilepsy especially in the presence of previous history of psychosis.\(^{18,19}\) The hypothesized mechanism of vigabatrin action in convulsion is selective suicide inhibition of the enzyme GABA-T, however, many studies show that there is no simple association between brain GABA content and convulsive activity.\(^{8,11,20}\) The degree of inhibition of GABA-T has, however, been reported to correlate with some other pharmacologic effects such as control of appetite, alcohol intake and sedation (see below). Vigabatrin develops, in some patients (less than 5%), headache, dizziness, nervousness, depression, memory disturbances, speech disorder, aggression, vertigo, vision abnormalities, confusion, insomnia and impaired concentration.\(^{21}\) Psychotic reactions, sedation and weight increase are the most common side effects reported in humans on long use with, interestingly, microvacuoles was not in man even after long term use.\(^{19,22}\) Long-term efficacy of vigabatrin in children seems to be stable in most patients.\(^{22}\) The major toxicological problem found in animals seen on neuropathological examination, following chronic use is microvacuolation of the white matter of the brain but its use in epileptic patients is limited by the risk of retinopathy and associated peripheral visual field defects.\(^{18,23}\)
Pharmacokinetic of vigabatrin

Human pharmacokinetic data indicate that vigabatrin is absorbed orally with bioavailability of 80-90% without protein binding and almost with no metabolic transformation. Half-life of vigabatrin in young adults is about six hours and 11 hours in the elderly with excretion via kidney (see below). A number of human studies have shown a dose related increase of cerebrospinal fluid levels of free and total GABA.[2,3,8] In humans, it has been found that the half-life of biologic activity of vigabatrin is far longer than the elimination half-life. However, the duration of action is believed to be more a function of the GABA-T resynthesis rate; levels of GABA-T do not usually return to their normal state until six days after stopping the medication (irreversible mode of action). Interestingly, vigabatrin is not bound to serum proteins and to eliminate mainly by renal excretion in unchanged form, and the elimination is not markedly affected by concomitant medication plus interactions affecting vigabatrin serum concentrations were not yet reported. However, the only reported interaction is a decrease plasma concentration of phenytion. In rats, the author reported an interaction between barbiturate and vigabatrin. Vigabatrin increases the duration of sleeping induced by pentobarbitone and vigabatrin diminishes the anxiolytic effect of phenobrabitone in rats.[24,25]

Experimental studies of vigabatrin

In animals, vigabatrin is effective against audiogenic and strychnineinduced seizures.[22,26] However, according to the author experience, no protection against strychnine is found.[27] Vigabatrin also inhibit photogenically induced seizures in pigeons and retards the development of kindling.[12,28] Vigabatrin has a less protection against seizures induced by the GABA agonists such as picrotoxin and bicucculline.[27] However, it has a low degree of acute toxicity in animals but chronic treatment may cause convulsion in rats. This is probably due to negative feedback inhibition. Vigabatrin produces several effects, mainly related to the dose. In low doses, vigabatrin induces an anxiolytic-like effect and in high doses vigabatrin induces a decrease in motor activity, sedation, hypothermia, piloerection, ptosis but in very high doses catatonia is seen.[28,29]

Toxicology of vigabatrin

Very little data concerning teratogenicity of vigabatrin use. The available human data obtained from mono-therapy exposures to vigabatrin were inconsistent. The European Agency for the Evaluation of Medicinal Products reported that about 15% vigabatrin exposed
pregnancies had congenital malformations, of which about 65% were MCMs; but the evaluated women were exposed to other antiepileptic drugs which may indicate the high of MCM in poly-therapy.\[30\] In animal studies, one previous study using rabbits reported that low dose of vigabatrin (150 mg/kg/day) produced cleft palate in limited number of offspring but with higher dose, 200 mg/kg/day, more pups were affected (10%). This is may be due to a decrease in methionine. Other study stating that rats whose mothers had taken 250-1000 mg/kg/day had poorer performance behavior experiments, rats used 750 mg were less weight than the normal rats, and with 1000 mg, no survive found. In another species, pregnant mice were given 300-600 mg/kg/day of vigabatrin, once on one of the gestation days 7-12. The highest dose (600 mg/kg) was lethal to all mice but the lower doses did not produce maternal toxicity. Growth retardation, mandibular, maxillary hypoplasia and exomphalos have been observed in the malformed offspring of vigabatrin treated mother.

Data of the stained skeletons revealed hypoplasia of midfacial bones, stage-dependent increase in the frequency of cervical, lumbar ribs and rib fusion in the drug-treated fetuses. In this connection, with regard to valproic acid effects, it generates cortical and hippocampal malformations linked to cell migration defects, thus this may indicate that it is a common mechanism for the deleterious effects of antiepileptic drugs including vigabatrin on fetal brain development.\[31\]

**Other pharmacological effects**

Our group reported that vigabatrin has an anxiolytic-like effect in the elevated plus-maze test without developing tolerance to the anxiolytic after chronic treatment (14 and 28 days).\[32,33,34\] This model was pharmacologically and behaviorally validated as a measure of anxiety in the rodent. As it has previously been mentioned that an interaction between vigabatrin and phenobarbitone has behaviorally been observed in the elevated plus-maze test.\[18\] It also protects the animals from development of tolerance and dependence on diazepam with regard to the anxiolytic effect and motor activity.\[35\] In a recent study, vigabatrin was reported to reduce ethanol intake and increase water and food in mice.\[36\] The authors suggested that vigabatrin appears to be related to the ability of vigabatrin to potentiate the pharmacological effects of ethanol. Indeed, we previously reported in two different studies a two-fold increase in brain GABA-transaminase in rats treated chronically with ethanol acutely, sub-chronically for 14 weeks and chronically for 90 weeks.\[37,38\] Anticonvulsants have also been candidates for use in the treatment of addiction based on the hypothesis that seizure kindling-like mechanisms contribute to addiction. Fechtner et al.
reported in an eight week study that vigabatrin has been effective in the therapy of cocaine and/or methamphetamine dependence with no ocular adverse effects were observed. In a recent clinical trials investigating the effect of anticonvulsant drugs for cocaine dependence, no evidence has shown the clinical use of vigabatrin in the treatment of patients with cocaine dependence. They also suggested that vigabatrin cannot be considered first-, second- or third-line treatment for cocaine dependence.

In conclusion, vigabatrin seems a very valuable antiepileptic drug. However, since this drug is relatively introduced to the clinical use in some countries, no long-term toxicological experience has yet been well identified in man to further judge it.

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