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Review: Normal and Abnormal Central Nervous System GABA Metabolism in Childhood†

J. JAEKEN[1], P. CASAER[1], K. D. HAEGELE[2] and P. J. SCHECHTER[2]
[1]*Department of Paediatrics, University of Leuven, University Hospital Gasthuisberg, 49 Herestraat, B-3000 Leuven, Belgium*
[2]*Merrell Dow Research Centre, 16 rue d'Ankara, 67084 Strasbourg, France*

Summary: The metabolism and function of central nervous system GABA is briefly reviewed. Hereditary disorders of the GABA metabolism presenting in childhood are discussed with particular emphasis on the recently identified succinic semialdehyde dehydrogenase deficiency and GABA-transaminase deficiency, and on diseases associated with low CSF GABA which await further unravelling. Low CSF GABA concentrations are not always associated with convulsions. A separate section is devoted to the CSF as a tool in the diagnosis of these disorders. Finally, we present a few diagnostic and therapeutic guidelines.

This review is devoted to central nervous ststem GABA, mainly from a clinical point of view and with particular emphasis on GABA-related problems in childhood. In the first part, brain GABA metabolism and function are covered briefly. The second part deals with GABA in the CSF (main forms, optimal storage of CSF, analytical methods and control values). In the third and main part we report on literature data and personal experience with hereditary disorders of central nervous system GABA metabolism.

BRAIN GABA METABOLISM AND FUNCTION

Gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter, is present in high but variable concentrations in the central nervous system (CNS), predominantly in the grey matter (Perry *et al.*, 1971). The distribution of GABA in the brain is remarkably similar to that of glutamate decarboxylase (EC 4.1.1.15), the enzyme catalysing its synthesis from glutamate, itself an excitatory neurotransmitter (Figure 1) (McGeer *et al.*, 1971). Glutamate decarboxylase is a highly regulated enzyme which

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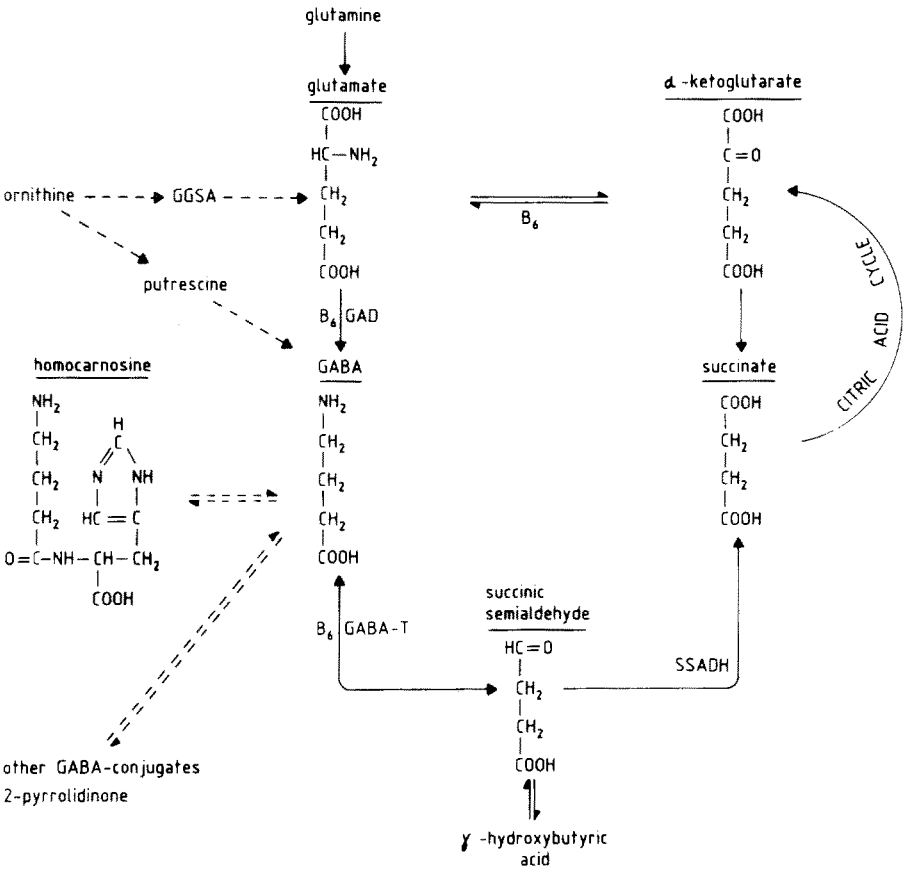

Figure 1 Schematic representation of the brain metabolism of GABA. B6: pyridoxal phosphate coenzyme. GGSA: glutamic acid-γ-semialdehyde. GAD: glutamic acid decarboxylase. GABA-T: GABA transaminase. SSADH: succinic semialdehyde dehydrogenase. Dotted arrows indicate reactions postulated, solid arrows indicate proven reactions

requires pyridoxal 5′-phosphate as cofactor. It is present in the brain in multiple molecular forms with different kinetic properties (Martin, 1987). Synthesis of GABA from ornithine via putrescine seems to be a minor pathway (Murrin, 1980; Daune and Seiler, 1988).

GABA modulates brain activity mainly locally, by release from interneurons. A number of longer GABA projection neurons are associated primarily with the basal ganglia and the cerebellum (Purkinje cells) (Fagg and Foster, 1983). GABA exerts its inhibitory action on CNS neurons by increasing the potential difference between the inside and the outside of the postsynaptic cell (Walker, 1983). On depolarization, neuronal GABA undergoes calcium-dependent release into the synaptic cleft. At the postsynaptic membrane, GABA binds to sodium-independent, high-affinity receptors present in the CNS of all vertebrates. Most GABA responses are mediated by $GABA_A$ receptors which increase the permeability of the postsynaptic membrane to the

chloride ion. They are blocked by the selective antagonist bicuculline. The structure of this receptor is now known in detail and genes for this receptor molecule have been cloned. The GABA receptor, a glycoprotein twining through the outer membrane of the postsynaptic cell, consists of two subunits (alpha and beta). Each subunit is a long chain of amino acids which includes four helical regions spanning the membrane and linear regions extending beyond it. The helical segments probably form a channel for chloride ions (Schofield *et al.*, 1987). Evidence has been obtained for the existence of a single protein complex carrying all the sites for $GABA_A$ agonists, benzodiazepines, channel-blocking ligands and barbiturates (Sigel *et al.*, 1984). It should be noted that although enhancement of the effects of the inhibitory neurotransmitter GABA is a major component of benzodiazepine action, the possibility has been raised that many of the actions of the benzodiazepines may involve adenosine (review in Phillis and O'Regan, 1988). $GABA_B$ receptors, on the other hand, are less abundant in the central nervous system than $GABA_A$ receptors. They are characterized by the binding of (−)-baclofen, are bicuculline insensitive and appear to regulate potassium channel activity (Strange, 1988). GABA is converted to succinate and oxidized in the tricarboxylic acid cycle through the successive actions of two enzymes: GABA-transaminase (EC 2.6.1.19) and succinic semialdehyde dehydrogenase (EC 1.2.1.24) (Figure 1). Both enzymes have a similar distribution pattern in human brain and are localized in the mitochondrial matrix.

Termination of GABA action is largely mediated by high-affinity uptake systems, in neuronal as well as in glial cells, which remove GABA from the synaptic cleft (Balcar *et al.*, 1979).

GABA IN CEREBROSPINAL FLUID

Besides free GABA, several other forms of GABA have been reported to occur in human CSF: GABA-peptides (mainly homocarnosine, GABA-lysine (Perry *et al.*, 1975) and GABA-cystathionine (Perry *et al.*, 1977)), N-carboxyethyl GABA (Fussi *et al.*, 1987) and 2-pyrrolidinone (Haegele *et al.*, 1987). Of these, homocarnosine and 2-pyrrolidinone are quantitatively the most important. 2-Pyrrolidinone, the cyclization product of GABA, accounts for essentially all of the so-called 'unidentified conjugated GABA', i.e. the difference between total GABA, and homocarnosine and free GABA. It may be a GABA precursor in the CNS and/or act as a pool for excess free GABA (Haegele *et al.*, 1987).

CSF GABA levels likely reflect brain GABA levels and are probably only minimally affected by changes in the peripheral GABA concentrations (review in Manyam and Hare, 1983). Most methods for determining GABA in brain tissue are insufficiently sensitive or specific for measuring the low free GABA levels in CSF. Three main methods have been used for this purpose: ion-exchange chromatography or reversed-phase liquid chromatography with fluorescence detection (Böhlen *et al.*, 1978; Goldsmith *et al.*, 1987) and radioreceptor assay (Enna *et al.*, 1977). The last method is non-specific and thus unreliable. CSF free GABA determination poses particular problems:

(i) Fractional collection of CSF specimens withdrawn by lumbar puncture shows lower GABA concentrations in the first (distal) specimens and higher concentrations in subsequent (proximal) specimens (Grove *et al.*, 1982a). Thus, valid comparisons are restricted to similar fractions.
(ii) Due to enzymatic homocarnosine degradation, GABA levels in the CSF show artefactual increases unless samples are deepfrozen within a few minutes (Grove *et al.*, 1982b) and stored at $-20°C$ when analysis is performed within a few weeks, and at $-70°C$ if the time elapsed between sampling and analysis is longer.

Considering these difficulties, Grove and colleagues (1983) have proposed using total GABA in CSF instead of free GABA as an indicator of changes in brain GABA function.

Literature data on lumbar CSF free GABA levels in control children is summarized in Table 1. Notably, children under two years of age have lower values than older children (Goldsmith *et al.*, 1987). Using ion-exchange chromatography, we have found that the lower limit of lumbar CSF free GABA levels in control children (showing mental retardation not associated with structural brain abnormality or known metabolic disorder) increases linearly from about 15 nmol/L in the neonatal period to about 65 nmol/L at the age of one year, and remains stable from then on. We found a similar evolution during the first year of life in CSF homocarnosine levels (an increase from 2.5 μmol/L to 6 μmol/L) and CSF total GABA levels (an increase from 4 μmol/L to 7 μmol/L) (unpublished data).

INHERITED DISORDERS OF CNS GABA METABOLISM

Disorders with increased CSF GABA concentrations

Two defects of the GABA catabolism have been reported: GABA-transaminase deficiency (Jaeken *et al.*, 1984; McKusick 13715) and succinic semialdehyde dehydrogenase deficiency (Jakobs *et al.*, 1981; McKusick 27198).

GABA-transaminase deficiency was found in a single Flemish family; the parents are related. The disease was associated with dysmyelination and was clinically characterized by extremely severe psychomotor retardation, pronounced hypotonia, convulsions and, contrary to most disorders with mental retardation, by length–growth acceleration due to hypersecretion of growth hormone. The patients (brother and sister) died at 1 and 2 years of age.

Table 1 Literature data on lumbar CSF free GABA levels in control children

Age in years (range)	*n*	*CSF GABA (mean ± SD)* (nmol/L)	*Method*	*Reference*
0.25– 2	10	98 ± 40	1	Goldsmith *et al.*, 1987
2–10	12	125 ± 23	1	Goldsmith *et al.*, 1987
2–12	21	101 ± 51	2	Perry *et al.*, 1988

Method 1: reversed-phase liquid chromatography
Method 2: ion-exchange chromatography with fluorescence detection

A 60-fold increase in GABA levels was noted in the CSF with only small increases in plasma concentrations and urinary excretion. Secondary to this GABA accumulation, there were also increases in the CSF concentrations of homocarnosine and other GABA compounds, and of ornithine and putrescine. CSF β-alanine was also increased, probably because this compound is an alternative substrate for GABA transaminase. It should be noted that a similar qualitative biochemical pattern (increases in GABA, GABA-conjugates and β-alanine) is also found in the CSF of humans treated with GABA-transaminase inhibitors such as γ-vinyl GABA, but here the relative increase in free GABA is much less pronounced (Grove *et al.*, 1981). The enzyme deficiency was demonstrated in lymphocytes, lymphoblasts and liver. The same defect was postulated to be present in brain as it is known that GABA transaminases of brain and peripheral tissues have the same properties. The pattern of occurrence suggested autosomal recessive inheritance in this family and this was confirmed by the demonstration of heterozygosity in lymphocytes and lymphoblasts of the parents and a healthy sibling (Gibson *et al.*, 1985). Therapeutic trials with pyridoxine, the coenzyme precursor of the enzyme, and with picrotoxin, a non-competitive GABA-antagonist, were unsuccessful.

GABA-transaminase is not expressed in fibroblasts (Gibson *et al.*, 1983), and thus prenatal diagnosis based on enzymatic analysis of amniotic cells is not feasible; however, activity is present in chorionic villus tissue (Sweetman *et al.*, 1986).

Succinic semialdehyde dehydrogenase deficiency has been documented in at least 15 patients (Jaeken *et al.*, 1988; Pattarelli *et al.*, 1988). Clinical features include non-progressive ataxia, hypotonia, mild to marked psychomotor retardation and, less frequently, hyperactivity, choreoathetosis and convulsions. The hallmark feature is the presence in urine, serum and CSF of γ-hydroxybutyric acid formed by the reduction of accumulating succinic semialdehyde (Figure 1). γ-Hydroxybutyric acid is a neuropharmacologically active compound. It is not detectable in the body fluids of control children (Gibson *et al.*, 1986). Lumbar CSF free GABA concentrations may (Gibson *et al.*, 1986) or may not be increased (Jaeken *et al.*, 1988) while CSF homocarnosine levels are increased. The enzyme deficiency has been demonstrated in lymphocytes and lymphoblasts (Pattarelli *et al.*, 1988). Enzyme activity is absent in control human fibroblasts, but present in chorionic villus tissue (Sweetman *et al.*, 1986). Genetic transmission is autosomal recessive. In an attempt to reduce the accumulation of γ-hydroxybutyric acid in a two-year-old Italian girl with this disease, we used the antiepileptic drug γ-vinyl GABA*. This substance is known to cause an irreversible inhibition of GABA-transaminase, the enzyme preceding succinic semialdehyde dehydrogenase (Figure 1). This treatment has now been given for 2.5 years and is accompanied by a significant and sustained clinical and biochemical improvement (Jaeken *et al.*, 1989).

Disorders with decreased CSF GABA concentrations

Hereditary diseases with low CSF GABA concentrations have been only poorly documented. *Pyridoxine-dependent convulsions* are considered to be due to brain

* Vigabatrin, Merrell Dow

GABA deficiency resulting from a genetic defect at the pyridoxal phosphate binding site of glutamate decarboxylase, the rate-limiting enzyme in GABA synthesis (Scriver, 1960). This disease satisfies the following criteria:

- onset of convulsions before, at or rapidly after birth;
- refractoriness to anticonvulsants;
- immediate response to pyridoxine;
- dependence on maintenance dose;
- no pyridoxine deficiency (Coursin, 1955).

Brain GABA has only been measured in one patient (Lott *et al.*, 1978) and CSF GABA in another patient (Kurlemann *et al.*, 1987); values were low in both. No data are available on CSF homocarnosine. Yoshida and colleagues (1971) presented evidence, but no definitive proof, of glutamate decarboxylase deficiency in their patient. This disorder is inherited as an autosomal recessive trait. Recently, atypical pyridoxine responsive convulsions have been reported in at least 13 children (Stephenson *et al.*, 1983; Goutières and Aicardi, 1985). This type of presentation differs from the classical form by its onset after the neonatal period, prolonged seizure-free intervals without pyridoxine and a higher incidence. These data indicate that a trial of pyridoxine should be performed in all seizure disorders with onset before 18 months of age, regardless of the type of convulsions. Inheritance is probably autosomal recessive.

During the last few years we have observed three infants with refractory neonatal convulsions, decreased CSF GABA but normal CSF homocarnosine concentrations. The possibility of a glutamate decarboxylase defect not involving the pyridoxal phosphate binding site is currently under investigation.

Recently we published a preliminary report on a boy with convulsions not responsive to pyridoxine, and low CSF GABA and homocarnosine concentrations (Jaeken and Casaer, 1987). The clinical picture also included pronounced psychomotor retardation, failure to thrive, axial hypotonia, peripheral hypertonia, ataxia and rotary nystagmus of both eyes. The convulsions were refractory not only to pyridoxine, but also to phenobarbital, phenytoin, γ-vinyl GABA and progabide. Clonazepam (0.1 mg/kg day), however, had a remarkable effect: seizures ceased, there was a regular weight gain and psychomotor development slowly progressed. Even more remarkable was the fact that the clonazepam could be progressively diminished and withdrawn after one year without recurrence of the seizures, in spite of persistently low lumbar CSF free GABA levels (30 nmol/L at the age of 3 years; range in age-matched controls 65–150). A noteworthy biochemical finding was an abnormally high increase in aspartate after acid hydrolysis of the CSF (80–120 μmol/L; control range 13–40), which proved to be due, in part, to *N*-acetylaspartate. We have seen the same biochemical picture (low CSF free GABA and homocarnosine, and abnormally high increase in aspartate after acid hydrolysis) in two sisters with a similar clinical syndrome but without convulsions and nystagmus. Their parents are related; the data suggests autosomal recessive inheritance. Liver glutamate decarboxylase activity was normal in all three children. Further biochemical investigations are in progress to reveal the basic defect of this intriguing disorder.

Finally, we have observed low CSF GABA and homocarnosine concentrations in two boys aged 3 and 7 years with metachromatic leukodystrophy, a genetic lysosomal disease due to arylsulphatase A deficiency. In the younger patient lumbar CSF free GABA was 32 nmol/L (control range 65–150) and homocarnosine 2.5 μmol/L (control range 6–10), and in the older patient the levels were 25 nmol/L and 0.9 μmol/L, respectively (control range for homocarnosine at this age 4–8). Both children had a pronounced spasticity which improved significantly during treatment with the GABA-transaminase inhibitor γ-vinyl GABA (50 mg/kg day) (Jaeken *et al.*, 1989). Several questions remain to be answered: are these abnormalities a constant finding in metachromatic leukodystrophy? Are they present in other leukodystrophies? We have seen this also in Krabbe disease. What is their pathogenesis (low functional activity or loss of GABA neurons, secondary enzymatic inhibition, ...)?

CONCLUSION

Although the GABA metabolism is a focus of intensive research, it remains a neglected area from the clinical point of view. This is at least in part due to problems in measuring the low CSF GABA levels. Literature data and our experience permit us to recommend a few diagnostic and therapeutic guidelines:

(i) CSF should be analysed for homocarnosine and GABA, and for amino acids before as well as after acid hydrolysis, in all unexplained brain disease;
(ii) Pyridoxine should be tried in all unclear seizure disorders with onset before 18 months;
(iii) A trial with benzodiazepines is indicated in refractory epilepsy.

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ERRATUM

Guest Editorship

Dr D. P. Brenton organized the symposium and acted as an editor for the publication on Maternal Phenylketonuria, Vol. 13 pp. 617–671.

Dr W. Endres and Dr Y. Shin were the Guest Editors for the Reviews and Short Communications from the 27th Annual Meeting of the SSIEM, Munich, 1989, published in Vol. 13 issues 3 and 4.