Inhibitory and excitatory neurotransmitters in the cerebrospinal fluid of epileptic dogs

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**Objective**—To determine concentrations of excitatory and inhibitory amino acids in CSF of a large number of dogs with idiopathic epilepsy or genetic epilepsy and to evaluate changes in CSF amino acid concentration with regard to drug treatment and sex.

**Animals**—35 Labrador Retrievers with genetic epilepsy (20 male and 15 female), 94 non-Labrador Retrievers with idiopathic epilepsy (71 male and 23 female), and 20 control dogs (10 male and 10 female).

**Procedure**—Collection of CSF was performed >72 hours after the occurrence of seizures. Cerebrospinal fluid concentrations of γ-aminobutyric acid (GABA), glutamate (GLU), aspartate (ASP), serine, and glycine were determined by use of high performance liquid chromatography with electrochemical detection.

**Results**—CSF concentrations of GABA and GLU were significantly lower in Labrador Retrievers with genetic epilepsy (LR-group dogs) than in control-group dogs or in non-Labrador Retrievers with idiopathic epilepsy (non–LR-group dogs). The GLU-to-GABA ratio was significantly higher in LR-group dogs than in non–LR-group dogs. CSF concentrations of GLU and ASP were significantly lower when all dogs with epilepsy (non–LR- and LR-group dogs combined) were compared with control-group dogs.

**Conclusions and Clinical Relevance**—A decrease in CSF concentrations of GABA appears to play a role in the pathogenesis of genetically determined epilepsy in Labrador Retrievers. However, this decrease in CSF concentrations of GABA may also be a consequence of seizures. Activity. The GLU-to-GABA ratio may prove to be a useful indicator of genetic epilepsy in Labrador Retrievers. (Am J Vet Res 2004;65:1108–1113)

Clinical studies on epilepsy in dogs have received considerable attention in recent years, and the disorder has been shown to be widespread in the canine population. Although inheritance appears to play an important role in the transmission of epilepsy in dogs, the precise pathophysiological characteristics of the disorder are poorly understood. Proposed pathophysiologic mechanisms in human epilepsy include changes in neurotransmitter function, neurotransmitter concentration, alterations in the expression of receptor or transmitter transporters, and changes in function of ion channels or enzymes involved in neurotransmitter metabolism. Although results of a study on neurotransmitters in the CSF of epileptic dogs have been published in recent years, Loscher and Schwartz-Porsche found low CSF concentrations of GABA in dogs with generalized tonic-clonic seizures and recently, Podell and Hadjiconstantinou reported similar findings in 19 dogs with idiopathic epilepsy. Glutamate (GLU), a major excitatory neurotransmitter in the CNS, has been shown to exert its action through a variety of presynaptic and postsynaptic receptors. It was found to play an important role in the initiation, spread, and maintenance of epileptic activity and focal injections of GLU antagonists alter the course and spread of seizure activity. Moreover, when GLU is present in high extracellular concentrations, an excitatory effect may be observed that appears to be induced by an increase in intracellular calcium ion concentrations and activation of enzymes, including proteases, phospholipases, nitric oxide synthases, and endonucleases, which contribute to cell death. In addition, other amino acids may play a role in the pathophysiologic findings of epilepsy in dogs such as the excitatory neurotransmitter aspartate (ASP) and the inhibitory transmitters, glycine (GLY) and serine (SER), which are metabolically linked to GLU. The purpose of the study reported here was to compare the CSF concentrations of both excitatory and inhibitory amino acids in the CSF of a large number of non-Labrador Retrievers with idiopathic epilepsy (non–LR-group dogs) and Labrador Retrievers with genetic epilepsy (LR-group dogs).

**Materials and Methods**

**Animals**—The medical records of dogs referred to the Division of Clinical Neurology at the University of Bern between 1993 and 2000 were reviewed. Criteria for inclusion in the study were a history of >1 episode of seizure activity and no abnormalities found on physical and neurologic examinations or on evaluation of a CBC, serum biochemical examination, or electroencephalogram.

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profile, urine analysis, or CSF analysis. A serum bile acid study was performed in all dogs included in this study to exclude dogs with portosystemic shunts.

In total, 129 dogs with epilepsy were included in the study. These dogs were placed into 2 groups: the first group of 94 dogs included non-LR-group dogs, and the second group of 35 dogs included LR-group dogs. The LR-group dogs came from a defined population with a polygenic recessive mode of inheritance of epilepsy that has been recently described.11,25

The first group of dogs (ie, non-LR-group dogs) consisted of 71 males (9 castrated and 62 sexually intact) and 23 females (14 spayed and 9 sexually intact) Labrador Retrievers ranging in age from 10 months to 11 years old (mean, 4.34 years old; 1 dog < 1 year old, 25 dogs 1 to 3 years old, and 9 dogs ≥ 6 years old). Fourteen of 35 dogs in this group had been treated with antiepileptic drugs for up to 2 weeks (range, 10 to 14 days) at the time of examination.

Dogs in the second group (ie, LR-group dogs) consisted of 20 male (8 castrated and 12 sexually intact) and 15 female (7 spayed and 8 sexually intact) Labrador Retrievers ranging in age from 10 months to 11 years old (mean, 4.06 years old; 2 dogs < 1 year old, 65 dogs 1 to 5 years old, and 27 dogs ≥ 6 years old). Forty-two of these dogs had been treated with antiepileptic drugs for up to 2 weeks (range, 10 to 14 days) at the time of examination.

All dogs (14 Labrador Retrievers and 42 non-Labrador Retrievers) that had been treated with antiepileptic drugs received phenobarbital orally at a dosage of 2 mg/kg twice daily. Mean serum concentrations of phenobarbital, measured 4 hours after drug administration, ranged from 20 to 45 µg/mL.

In addition, 20 dogs that served as control-group dogs were included in the study. The control group consisted of 20 healthy 1-year-old Beagles (10 sexually intact males and 10 sexually intact females) that had served as a control population in another study. Blood sample collection was performed under general anesthesia, shortly before the dogs were euthanatized. Histologic examination at the time of necropsy, including routine CNS evaluation, in these dogs revealed no abnormalities.

Determination of amino acid concentrations in CSF—Collection of CSF was performed by puncture of the cerebellomedullary cistern under general anesthesia (premedication with diazepam [10 mg/mL] and induction and maintenance with propofol). Collection of CSF was performed > 72 hours after the occurrence of seizures. Cerebrospinal fluid samples were immediately stored at −70°C pending further analysis.

Analyses by use of high performance liquid chromatography (HPLC) were performed following thawing of the CSF samples. Each sample was thawed once and 1 aliquot was used without further dilution for analysis of GABA while another aliquot (30 µL) of CSF was immediately deproteinized by adding a mixture of internal standard (L-homocysteic acid; final concentration of 1.25 nmol/mL) and methanol and allowing it to stand for 5 minutes. Samples were then centrifuged at 20,800 × g for 10 minutes. For repeated determinations of amino acid concentrations, the sample was thawed once and 1 aliquot was used without further dilution for analysis of GABA while another aliquot (30 µL) of CSF was diluted with 7 parts of methanol and used for detection of all other amino acids (internal standard; final concentration of 1.25 nmol/mL). Analysis of GABA was based on the procedure of Löschter et al and detection of all other amino acids was based on the procedure of Halawa et al.

Supernatants were injected into glass vials and placed in an autosampler for automatic injection. For precolumn derivatization, 50 µL of o-phthalaldehyde was added, followed by an injection into a C18 column.

The HPLC system consisted of a pump, a fluorometer, and an autosampler. The resolution of the amino acids (GABA, GLU, ASP, SER, and GLY) was accomplished by use of a multi step gradient elution. Elution solvent A consisted of 90% phosphate buffer (0.015M), 5% tetrahydrofuran, and 5% methanol. Elution solvent B consisted of 40% phosphate buffer (0.015M), 13% acetonitrile, and 43% methanolic solution. Water used in the preparation of elution solvents was passed through a purification system. The flow rate was set at 0.8 mL/min. To identify the various amino acids, a standard solution of known amino acids was used. The standard was measured several times each day at different concentrations and used for each amino acid determination.

A fluorescence detector (excitation wavelength = 340 nm, emission wavelength = 450 nm) was used for derivative detection. Each sample was injected 4 times (ie, diluted and nondiluted, replicates) because the limited linearity of fluorometric detection did not allow determination of the low concentrations of GABA (detection limit, 30 pmol/mL) and the much higher concentrations of the other amino acids in the nondiluted sample in a single run. Within a running time of 55 minutes, ASP, GLU, SER, GLY, and GABA were quantified according to their retention time by use of a software program.

Statistical analysis—Statistical analysis was performed by use of a software program. An ANOVA was used for overall analysis in the measured CSF concentrations of GLU, GABA, and ASP to test intergroup differences. In addition, an ANOVA was performed to individually test the effects of sex and drug treatment on CSF concentrations of amino acids. The Bonferroni adjustment for multiple comparisons was used whenever > 2 groups were included in the analysis. Values of P ≤ 0.05 were considered significant. All values are expressed as means ± SEM.

Figure 1—Mean ± SEM CSF concentrations (nmol/mL) of γ-aminobutyric acid (GABA; panel A) and glutamate (panel B) in control dogs (n = 20), Labrador Retrievers with genetic epilepsy (LR), non-Labrador Retrievers with idiopathic epilepsy (Non-LR), and all dogs with epilepsy (either idiopathic or genetic epilepsy; 129). LR = Labrador Retrievers with genetic epilepsy. Non-LR = Non-Labrador Retrievers with idiopathic epilepsy. Values of P ≤ 0.05 represent significant differences between groups.
Results
Comparison of CSF amino acid concentrations in non–LR-group dogs and LR-group dogs—The CSF concentration of GABA was significantly lower in LR-group dogs, compared with control-group dogs and non–LR-group dogs (Figure 1). No significant difference in CSF concentration of GABA was found between control-group dogs and all dogs with epilepsy (non–LR- and LR-group dogs combined). Cerebrospinal fluid concentrations of GLU were found to be significantly higher in control-group dogs, compared with LR-group dogs and all dogs with epilepsy (non–LR- and LR-group dogs combined). No significant difference in CSF concentration of GLU was found in control-group dogs, compared with non–LR-group dogs.

The CSF concentration of ASP was lower in LR-group dogs and non–LR-group dogs, compared with control-group dogs, but the effect was not significant. A significantly different CSF concentration of ASP was only obtained when all dogs with epilepsy (non–LR- and LR-group dogs combined) were compared with control-group dogs (Table 1). Cerebrospinal fluid concentrations of GLY were significantly lower in non–LR-group dogs than in LR-group dogs, but were not significantly different from control-group dogs.

Comparison of CSF concentrations of amino acids between males and females—Differences between males and females in CSF concentrations of GLU were only found in LR-group dogs, in which

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*Significantly different from values for control group dogs at P < 0.05, 0.01, and 0.001, respectively.
†Significantly different from values for LR-group dogs at P values < 0.05 and 0.001, respectively.
‡95% confidence limit. GABA = γ-Aminobutyric acid. GLU:GABA = Glutamate-to-GABA ratio. CG = Control-group dogs. LR = Labrador Retrievers with genetic epilepsy. Non-LR = Non-Labrador Retrievers with idiopathic epilepsy.

The GLU-to-GABA ratio (Table 1) was significantly higher in LR-group dogs than in non–LR-group dogs. No significant difference in the GLU-to-GABA ratio was obtained when LR-group dogs were compared with control-group dogs. Furthermore, no significant difference in this ratio was found when all dogs with epilepsy (non–LR- and LR-group dogs combined) were compared with control-group dogs.

Comparison of CSF concentrations of amino acids between males and females—Differences between males and females in CSF concentrations of GLU were only found in LR-group dogs, in which
females (0.377 ± 0.015 nmol/mL) had significantly lower concentrations than males (0.475 ± 0.018 nmol/mL). For CSF concentrations of ASP, differences between males and females were only observed in control-group dogs, for which females (0.162 ± 0.043 nmol/mL) had significantly lower CSF concentrations than males (0.120 ± 0.043 nmol/mL). No significant differences were found between males and females in CSF concentrations of any of the neurotransmitters when all dogs with epilepsy (non–LR- and LR-group dogs) were combined.

Comparison of CSF concentrations of amino acids in treated and untreated dogs—The CSF concentrations of GLU, GABA, and ASP measured in non–LR- and LR-group dogs were determined (Figure 2). No differences in amino acid concentrations of dogs treated with phenobarbital were seen in LR-group dogs, compared with control-group dogs. Cerebrospinal fluid concentrations of GABA, GLU, and ASP CSF were significantly lower in non–LR–LR-group dogs treated with phenobarbital, compared with untreated non–LR–LR-group dogs. Treatment with phenobarbital did not result in differences in CSF concentrations of GABA and GLU when all treated non–LR- and LR-group dogs were compared with all untreated non–LR- and LR-group dogs. However, all treated dogs with epilepsy had significantly lower CSF concentrations of ASP compared with all untreated dogs with epilepsy.

Discussion

Our study investigating amino acid concentrations in the CSF of non–LR- and LR-group dogs differs from previously reported clinical studies in both the large number of dogs with epilepsy included and ancillary measurements of CSF concentrations of ASP, SER, and GLY. Inclusion criteria for dogs of our study in the non-LR group were 3 fold. Firstly, dogs in the non-LR group had to have a history of >1 episode of seizure activity. Podell and Hadjiconstantinou reported that changes in GABA and GLU concentrations in the CSF were independent of time elapsed between the first observed seizure and CSF sample collection. Secondly, dogs had to have no abnormalities on physical and neurologic examinations. Thirdly, dogs had to have values that were within reference range on CBC determination and serum biochemical, urine, and CSF analyses. The 35 dogs of the LR group in our study were clinically evaluated as previously described. Our main objective was to find possible associations between CSF concentrations of amino acids and epilepsy in Labrador Retrievers and non-Labrador Retrievers.

In our study, the finding of decreased CSF concentrations of GABA in LR-group dogs, compared with control-group dogs, is in agreement with results of previous reports in the veterinary and human literature. Both experimental and clinical evidence exists that suggests that GABA exerts an important role in the mechanism and treatment of epilepsy. Abnormalities in GABAergic function have been observed in genetic and acquired epilepsy in animals: GABA agonists suppress seizures, GABA antagonists produce seizures, and drugs that inhibit GABA synthesis cause seizures. Decreased activity of glutamic acid decarboxylase (GAD), an enzyme found as 2 isofoms in the cell body and nerve terminals that synthesizes GABA via decarboxylation of L-GLU, may result in decreased CSF concentrations of GABA. The activity of GABA in brain biopsy specimens from humans with epilepsy was found to be low, which would appear to support the hypothesis that alterations in the GABAergic system occur in epilepsy. In our study, impairment of GAD activity may explain the low CSF concentration of GABA in LR-group dogs. During et al. reported relatively low CSF concentrations of GABA preceding the onset of a seizure and a significant but delayed increase in CSF concentrations of GABA during seizure activity. This may result from a nonvesicular mechanism in which the extracellular GABA concentrations increase in response to excessive release of GLU. The low CSF concentration of GABA found in LR-group dogs of our study (Figure 1) supports the hypothesis that impairment of GABA function is involved in seizure activity. This is of particular interest because CSF concentrations of GABA in LR-group dogs were not only found to be significantly decreased, compared with control-group dogs, but also compared with non–LR-group dogs. In addition to a decrease in GABA activity in interneurons of discrete regions of the cortex or hippocampus of epileptics and a decrease in the number or efficiency of GABA transporters, GABA degradation might also be altered in Labrador Retrievers that have genetic epilepsy. However, CSF neurotransmitter concentrations cannot be interpreted as a direct index of synaptic activity of these neurotransmitters. Limitations exist on the use of brain microdialysis in directly detecting synaptic GLU and GABA concentrations. However, evidence suggests that extracellular concentrations of GABA and GLU correlate with the functioning of neuron-astrocyte networks with regard to physiologic and pathophysiologic characteristics of epilepsy. Glutamate and GABA are suggested to have functional properties different from those of their receptors located at the synapse.

In our study, decreased CSF concentrations of GLU in LR-group dogs were found in comparison to control-group dogs, but no significant difference in CSF concentrations of GLU was found in non–LR-group dogs, compared with control-group dogs (Figure 1). Low CSF concentrations of the excitatory neurotransmitter ASP were obtained in LR- and non–LR-group dogs, but the decrease in ASP was only significant when all dogs with epilepsy (non–LR- and LR-group dogs combined) were compared with control-group dogs. Similar results have been reported in human patients with epilepsy.

Podell and Hadjiconstantinou reported an increase in CSF concentrations of GLU in dogs with idiopathic epilepsy. By comparing the CSF concentrations of GLU of the control-group dogs of our study with those of that study, we found substantially higher CSF concentrations of GLU in the control group of our study (our study, range, 548 to 740 pmol/mL; study of Podell and Hadjiconstantinou, range, 50 to 270 pmol/mL), which may explain the difference in results between the 2 studies.
During and Spencer showed that GLU is responsible for the initiation of epileptiform activity and that CSF concentrations of GLU measured by microdialysis probes in the hippocampus in epileptic patients were higher before seizure onset. The release of GLU preceded the actual seizure by 1.5 minutes. Events contributing to an increase in extracellular GLU before or at seizure onset are not known. Possible mechanisms include a causal sequence involving enhanced release or impaired uptake of the amino acid and enhanced activation of postsynaptic GLU receptors. Changes in CSF concentrations of GLU prior to and during seizure activity were also reported in rats in which decreased CSF concentrations of GLU were measured in the hippocampus and hypothalamus during the preictal period and in the substantia nigra and caudate putamen during seizure activity. However, a decrease in CSF concentrations of GABA accompanied by a decrease in GLU concentrations has been reported by Nitsch et al following seizure induction by systemic convulsants. One hypothetical explanation for our finding of a decrease in CSF concentrations of GLU is that transient alterations of GLU transporter expression, which has been shown to occur in stimulated regions such as amygdala and piriform cortex, may be responsible for the genesis of seizure activity. This could also be true for the LR-group dogs of our study, which had significantly decreased CSF concentrations of GLU, compared with control-group dogs and non–LR-group dogs. These findings indicate that the CSF concentrations of GLU, as well as GABA, play an important role in genetic epilepsy of the Labrador Retrievers of our study, but whether it is a cause or the consequence of seizure activity, the pathophysiologic condition, or both cannot be concluded.

The low GLU-to-GABA ratio in the non–LR-group dogs of our study supports the hypothesis that an imbalance between GABAergic inhibition and excitation by glutamate is involved in epileptogenic processes. It has been proposed that an imbalance between excitatory and inhibitory synaptic transmission that favors excitation leads to the initiation of epileptic discharges. A quantitative imbalance between excitatory amino acids (ie, GLU) and inhibitory neurotransmitters (ie, GABA) could cause refractory seizures. The excitatory-to-inhibitory amino acid ratio has been shown to be higher in synaptosomes in abnormal brain parenchyma of human patients with epilepsy. Because the GLU-to-GABA ratio was found to be significantly higher in LR-group dogs, compared with non–LR-group dogs of our study, this ratio may be a useful indicator of genetic epilepsy in Labrador Retrievers.

In our study, CSF concentrations of SER were significantly increased in non–LR-group dogs, compared with control-group dogs and LR-group dogs. The significance of the disparities between the CSF concentrations of GLY and SER in non–LR-group dogs is unclear and, to our knowledge, no studies on the potential role of these amino acids in epilepsy in dogs have been reported previously. However, evidence from human and rodent studies suggests that SER and GLY are involved in the pathogenesis of epilepsy. In rats with chronic epilepsy, GLY, which is known to potentiate glutamatergic transmission, has been reported to be increased in several brain regions. In rats with chronic focal epilepsy, the interictal CSF concentrations of SER were shown to be significantly higher at the lesion side, compared with the contralateral cortex. In our study, treatment with anticonvulsant medication (phenobarbital) over a short period did not affect GABA concentrations in the CSF of LR-group dogs, corroborating previous findings by Löscher and Schwarz-Porsche. However, treatment of non–LR-group dogs resulted in a significant decrease in CSF concentrations of GABA, GLU, and ASP. In contrast to the findings in our study, Podell and Hadjiconstantinou reported no correlation between CSF concentrations of GLU, GABA, and GLU-to-GABA ratio and the total number of seizures recorded before or after initiation of phenobarbital treatment in dogs.

In summary, low CSF concentrations of GABA in the LR-group dogs of our study suggest a key role of GABA in genetically determined seizures. Whether these findings are causally related to seizure induction or are partly or entirely secondary to the seizure activity cannot be concluded. Moreover, our finding of similar CSF concentrations of GABA in treated and untreated LR-group dogs may indicate that this decrease is more likely to reflect the pathogenesis of the disease than a consequence of the disease. Further clinical studies are needed to evaluate the role of GLY and SER in dogs with epilepsy and investigate a potential diagnostic application of determining CSF concentrations of amino acid neurotransmitters in various forms of epilepsy, including primary, genetic, and secondary forms.

References

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