Seizure activity is associated with a wide range of local biochemical changes affecting, among others, amino acid neurotransmitters. Several studies have shown local changes in transmitter amino acid levels after status epilepticus induced by systemic administration of several chemoconvulsants. Furthermore, local changes in amino acid levels have been demonstrated in the kindling model of epilepsy. We studied the local changes in transmitter amino acids in partial and secondarily generalized seizures after picrotoxin microperfusion in rat hippocampus.

We used a CMA/120 system for freely moving animals. Rat hippocampus was perfused with Ringer’s solution through CMA/12 microdialysis probes at a flow rate of 2 µl/min for 3 h with continuous EEG and video tape recording. Dialysate samples were taken every 15 min. After 2 h, a picrotoxin solution (100–300 µM) was substituted for Ringer’s solution for 5 min. Samples were analyzed by liquid chromatography with fluorescence spectrophotometry labelling with 6-phthalaldehyde and N-acetyl-L-cysteine. The same experimental protocol was repeated as many as four times in each rat, with 1-week intervals.

The effect of picrotoxin perfusion on γ-aminobutyric acid (GABA), glycine, aspartate, glutamate, and taurine extracellular concentrations from consecutive dialysate samples were assessed by one-way analysis of variance. Amino acid level showed a significant decrease (p < 0.05) in aspartate, glutamate, and glycine. However, no alterations were noted in extracellular GABA and taurine levels. No significant differences between basal concentrations for each rat were evident after several probe introductions. (Supported by Grant UXGA 20805A95 from Xunta de Galicia, Galicia, Spain.)


Neuronal activities were recorded intracellularly in neocortical slices obtained from rats with GABA-withdrawal syndrome (GWS), a focal epilepsy consequent to interruption of a chronic GABA infusion into the rat somatosensory cortex. In the epileptic focus area, 80% of neurons showed intrinsic bursts induced by depolarization and/or paroxysmal depolarization shifts (PDS) induced synaptically. Bursts and PDS are generated by Ca2+-dependent plateau potentials and are terminated by a K+ current highly sensitive to tetraethylammonium. Noradrenaline (NE) applications during GWS produced slow depolarization resulting from reduction of a potassium current and additional paradoxical effects not observed in normal cortex. First, in nonbursting neurons, NE caused the appearance of intrinsic bursts related to an increased depolarization and to an NE-activated Ca2+ inward current. Second, in bursting neurons, NE shortened PDS, increased afterhyperpolarizations, and facilitated the appearance of extrabursts, determining their frequency to ≥5 Hz. This extraburst frequency corresponds to that of EEG spikes of GWS. Moreover, evidence of inactivation of the Ca2+ current underlying bursts was obtained in neurons with intrinsic bursts during the NE-induced depolarization. These paradoxical effects of NE during GWS are in keeping with immunocytochemica and in situ hybridization studies showing an overexpression of neuronal NE in the epileptic focus area.

Basic Neurophysiological Mechanisms of Epilepsy. T. S. Stepanova, E. Ya. Gurevich, K. E. Lebedev, and V. P. Bersnev (St. Petersburg, Russia).

We analyzed material from patients submitted to surgical treatment (including the use of intracerebral electrodes) in 200 patients with focal and generalized epilepsy. Patterns of slow ongoing activity [EEG, electrocorticography (ECoG), stereo-EEG], brainstem auditory evoked potentials (BAEP), and visual EP were studied. According to the conceptual electrophysiologic model of epilepsy (T. S. Stepanova, 1968–1971), the development of the disease has the following stages: “epileptic” neuron → epileptogenic focus → epileptogenic system → “epileptic brain.” At stage II, the critical volume of neuronal population capable of functioning as a triggering focus is 1010–1011 cells (microsystems). At stage III, veically organized systems of the discharge reverberation were evident in generalized epilepsy, and horizontally organized systems were evident in focal epilepsy (macrosystems). The peculiarities of interpeak BAEP latency at the pontomesencephalic level in primary and secondarily generalized seizures were noted in contrast to partial seizures. Visual EP in epilepsy take the form of “peak-and-wave” complexes. Stereo-EEG monitoring of nocturnal slow-wave and REM sleep facilitated study of the precise structure and mechanisms of ictal and pontine inhibitory systems controlling epileptogenesis. The conditions influencing discharge generalization or cessation and those influencing (electrosubcortical stimulation) epileptic activity and inhibitory systems are considered.

Effects of ACTH1-24 on GABA Receptor Complex in Rat Brain. Hisaki Tanoue, Takashi Mimaki, and Makoto Mino (Department of Pediatrics, Osaka Medical College, Takutaki City, Osaka, Japan).

Adrenocorticotropic hormone (ACTH) has clinical efficacy for some neurologic disorders, especially seizure disorders of childhood such as infantile spasms (IS). To analyze the anticonvulsve mechanism of ACTH, we investigated the effects of ACTH1-24 on γ-aminobutyric acid (GABA)-stimulated [35Cl]-uptake, [3H]-butyrylchlolephosphorochoelinate (TBPS) binding, on [3H]GABA binding and on [3H]diazepam (DPZ) binding in rat cerebrocortical membranes in vitro.

ACTH1-24 showed a dose-related inhibition of net uptake of [35Cl]-. The maximal inhibition of ACTH1-24 was obtained at a concentration of 10 µM. ACTH1-24 had a dose-related enhanced effect on [3H]TBPS binding in the presence of 1 µM exogenous GABA. The enhanced effect of ACTH1-24 on [3H]TBPS binding was 42.3 ± 0.8% at a concentration of 100 µM. ACTH1-24 did not have a significant effect on [3H]GABA binding at concentrations of 0.1 and 1 µM. However, at concentrations of 10 and 100 µM, ACTH1-24 showed a statistically significant inhibitory effect on [3H]GABA binding; 15.0 ± 0.7% and 27.0 ± 2.1% inhibition as compared with control, respectively. ACTH1-24 also tended to have an inhibitory effect on [3H]DPZ binding. Our results suggest an antagonistic effect of ACTH1-24 on GABA, receptor which may correlate with the potential proconvulsant activity.

Role of Sex Hormones in a Model of Generalized Absence Epilepsy. G. Van Luijtenaar, Franz Van Haaren, and Ris Dirksen (NICT/Department of Psychology, University of Nijmegen, Nijmegen, The Netherlands).

Sex hormones play a role in epilepsy. Estrogens are believed to be proconvulsant, and androgens are believed to have weak anticonvulsant properties. Little is known about these hormones in absence epilepsy, in which females have a slightly worse prognosis. A role of sex hormones in absence epilepsy is suggested because near puberty, absence epilepsy develops into more serious forms of epilepsy. In the present study, the role of circulating
sex hormones was investigated in a genetic model of generalized absence epilepsy.

Forty-eight WAG/Rij rats served as subjects: 24 males and 24 females. At age 3 months, 12 males and 12 females were gonadectomized under anesthesia; the other 24, 12 in each group, were sham operated. At age 6 months, under anesthesia, all rats had EEG electrodes implanted. One week later, EEGs were recorded, and spike-wave discharges (SWD) were counted.

The four groups of WAG/Rij rats differed in the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD: ovariectomy decreased and castration increased the number and duration of the spontaneous occurring SWD:

Effects of Intrahippocampal Injections of Muscimol and Bicuculline on Spike-Wave Discharges and Frequency Spectra in Rats. C. van Rijn, Sabine Gijzen, and E. L. J. M. van Luijtenbali (NICI/Department of Psychology, University of Nijmegen, Nijmegen, The Netherlands).

γ-Aminobutyric acid (GABA) is differentially involved in convulsive and nonconvulsive epilepsy: Peripheral administration of GABA agonists inhibits convulsions but facilitates spike-wave discharges. Intracerebroventricular injections with muscimol or THIP also facilitates spike-wave discharges (SWD). The lateral part of the thalamus is involved in the genesis of SWD, it receives and projects to the reticular thalamic nucleus, the pseumecriner for EEG oscillations such as sleep spindles and SWD. We investigated the role of GABA in the ventropostero-lateral nucleus (VPL) of the thalamus and the relation between the antiabiosis effects and the spectral changes: Many antiepileptic drugs have a major effect on the spectral content of the EEG.

WAG/Rij rats were bilaterally implanted with cannulas in the VPL and with cortical EEG electrodes. Bilateral injections of solvent, 0.02 and 0.2 nmol/0.3 μl muscimol, and 0.15 nmol/0.3 μl bicuculline (BIC) were given alone or in combination. SWD and the spectral content of the cortical EEG were analyzed. Muscimol dose-dependently decreased the incidence and the number of SWD. After the higher dose, SWD were almost absent for 3 h. BIC slightly increased the duration of SWD and partially antagonized the effects of muscimol. Spectral analyses of the EEG showed a dose-dependent increase after muscimol in the delta band and a decrease in theta and beta power. BIC had no effect on the spectral content. Histological verification of the injection site confirmed that the cannulas were aimed at the VPL.

Liu et al. (1991) also reported suppression in the most lateral part of the thalamus, including the reticular thalamic nucleus. The significant dose-dependent suppression of the number and duration of SWD after muscimol administration may suggest that the membranes of thalamic relays cells become depolarized through GABAergic activation—probably of interneurons. This might prevent the occurrence of EEG oscillations. The dose-dependent changes in the frequency spectra were not antagonized by BIC, suggesting that different factors are involved in the suppressive effects of SWD and the changes in the EEG spectrum.

Endogenous Amino Acid Neurotransmitters in the Brains of Rats With and Without Spike-Wave Discharges. C. M. Van Rijn, A. Van Raay-Selten, E. Willems, R. Wevers, and E. L. J. M. Van Luijtenbali (Departments of Psychology/NICI and Anaesthesiology, University of Nijmegen, Nijmegen, The Netherlands).

WAG/Rij rats are regarded as a genetic model for human absence epilepsy because as they spontaneously show spike-wave discharges (SWD) in the EEG. An imbalance between excitation and inhibition may underlie the pathogenesis of SWD. We determined concentrations of several amino acid neurotransmitters in five brain regions in two strains of animals: WAG/Rij rats and ACI rats. The latter animals do not have SWD.

After rats were decapitated, the brains were removed (each strain n = 10). The hippocampus, striatum, mesencephalon, thalamus, and frontal cortex were dissected. The parts were homogenized. The total homogenate was analyzed by chromatography with an amino acid analyzer. Data were evaluated by analysis of variance.

All the amino acids determined showed regional concentration differences. Strain differences were also noted: in all areas tested, aspartic acid, glutamine, and glycine concentrations were lower in the WAG/Rij than in the ACI animals. Higher concentrations of taurine were present in the WAG/Rij than in the ACI strain, but only in the hippocampus and in the frontal cortex. No strain differences were noted in glutamic acid, serine, or γ-aminobutyric acid (GABA).

We suggest that excess inhibition mediated by GABA underlies the genesis of the SWD. However, the GABA content was not different in the two strains. The concentrations of amino acids that modulate excitation (including glycine) were lower in the WAG/Rij rats than in the ACI rats. The role of taurine in epileptogenesis is still unclear. Future research must clarify whether the observed differences are due to strain differences, are the cause of SWD, or are a secondary consequence of SWD. Nevertheless, our results show that the debate over the inhibition–excitation imbalance is not yet settled.


Recent evidence indicates that polysaturated fatty acids (PUFAs) derived from fish oil, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can prevent lethal ischemia-induced cardiac arrhythmias in animals and possibly also in humans. In isolated cardiac myocytes, EPA and other PUFAs decreased the excitability (i.e., increased action potential threshold and increased refractory period). The decreased excitability can be explained by the voltage-dependent decrease in sodium current and the shift in steady-state inactivation curve in a hyperpolarizing direction that has been demonstrated in these cells. If PUFAs had the same effect on central neurons, these compounds might be expected to exert an anticonvulsant effect. Several antiepileptic drugs have been shown to affect sodium currents, an action that may contribute to their anticonvulsant effect. We tested this possibility in the cortical stimulation model. Chronic cortical stimulation electrodes for determination of the convulsive threshold and intravenous and intraarterial cannulas for drug administration and blood sampling were implanted in rats. EPA or DHA was infused for 30 min, with albumin in physiological saline as carrier. EPA and DHA only moderately increased the threshold as compared with pretreatment baseline. After infusion, the threshold remained slightly increased for several hours and returned to baseline after 24 h. Vehicle alone did not affect the threshold.

The extent to which PUFAs affect sodium channels in isolated neurons is not known. Therefore, PUFAs may simply be less effective in the CNS than in heart cells. Alternatively, pharmacokinetic factors may have played a decisive role in our experiments and we may thus have failed to reach a sufficiently high free concentration in the brain to produce a clear antiepileptic effect. Further research is necessary to resolve these matters.

Opposite Effects of Kindling Epileptogenesis and Carbamazepine on Sodium Currents in Rat Hippocampus CA1 Neurons. M. Vreugdenhil and W. J. Wadman (Amsterdam, The Netherlands).

The whole-cell sodium current (I Na) and its modulation by carbamazepine (CBZ 15, 40, 100 μM) was studied in hippocampal neurons.