A new experimental model of epilepsy, described by Gross and Weaver [*J Cardiovasc Pharmacol* 1993;22(suppl 8):282–7] was studied. Endothelin-1 (ET), synthesized by O. Kaurov and M. Smirnova (Saint Petersburg) was administered into the lateral ventricle of rats. ET 9 pmol/2 μl was the threshold dose. High doses of ET induced death; lower doses were not effective. Behavior seizures and electrical activity of frontal cortex, amygdala, and hippocampus were recorded. Barrel rolling and generalized seizures were observed. Amygdala afterdischarges preceded the motor manifestations, which had a very short latency. Intraventricular administration of triol saponins of Korean red ginseng (before or after ET) and ginsenoside Rc inhibited the seizures and significantly increased latency. Inhibition of ET-1–induced barrel rolling and epileptic activity of limbic structures by intracerebroventricular pretreatment with ginseng was dependent on the interaction of ginsenosides with the GABA–benzodiazeine–chloride channel receptor complex (*Gen Pharmacol* 1994;25:193–9). Intranasal application of ET-1 in the same dose did not induce barrel rolling and seizures.

Catalepsy and Epilepsy in Rats: Common Factors? E. V. Petrova, E. L. J. M. van Luijtelaar, and G. D. Kuznetsova (Institute of Higher Nervous Activity and Neurophysiology, Moscow, Russia; and Department of Psychology, University of Nijmegen, Nijmegen, The Netherlands).

The cataleptic state is characterized by the presence of muscular rigidity, automatisms, and myoclonus. These symptoms frequently occur in epileptic patients. In animal models, a relation between catalepsy and epilepsy also is sometimes reported. Petrova et al. (*J Vysh Nervn Deyat* 1992;42:1009–17) showed that genetic cataleptic rats have an increased predisposition for epileptoform activity, including signs of petit mal. In the present study, we investigated whether WAG/Rij rats, genetically endowed with generalized spike-wave discharges (SWD) are more sensitive for catalepsy.

WAG/Rij and Wistar rats, implanted with chronic EEG electrodes, were recorded for 15 min; rats were exposed to photic stimulation of 3, 10, and 25 Hz for 2-min periods and several days later to acoustic stimulation with key ringing.

WAG/Rij showed some behavioral signs of fear after both types of stimulation, and the EEG was periodically driven by the rhythm of the flashes; SWD were not observed. However, in the first 5 min after the end of the visual and auditory stimulation, 10 and 11 of 13 WAG/Rij became motionless and retained an uncomfortable pose when forced to sit on their sacrum. The number of SWD gradually increased and reached a maximum 5–10 min after the end of the stimulation. Wistar rats remained active after visual and auditory stimulation and manifested no sign of pathology in behavior or in EEG. Genetically epileptic WAG/Rij are more susceptible than Wistar rats to induction of a cataleptic state, suggesting that the mechanisms responsible for SWD and for catalepsy might be related.

Effects of Remacemide and Its Metabolite FPL 12495 on Spike-Wave Discharges, EEG, and Behavior in Rats with Absence Epilepsy. E. L. J. M. van Luijtelaar and A. M. L. Coenen (NICI, Department of Psychology, University of Nijmegen, Nijmegen, The Netherlands).

Anticonvulsant drugs may or may not be effective against generalized absence epilepsy. Carbamazepine and phenytoin aggravate spike-wave discharges (SWD) whereas valproate and benzodiazepines reduce SWD. The effects of the new anticonvulsant remacemide on SWD are unknown, which prompted us to investigate the effects of remacemide and its active metabolite FPL 12495 in a genetic rat model for absence epilepsy, the WAG/Rij strain. Number and mean duration of SWD, parameters of the background EEG and spontaneous behavior were measured after various oral doses of remacemide and FPL 12495.

A decrease in the number of SWD was noted after remacemide administration. At the highest dose, SWD were almost completely suppressed and there were no important effects on behavior or on spectral content of the background EEG, suggesting that remacemide has few side effects and might be effective against absence epilepsy. A decrease in the number of SWD was also noted after FPL 12495 gavage, but mean duration was prolonged. Behavioral changes were apparent only after the highest dose, accompanied by changes in spectral content, suggesting that FPL 12495 has other central effects as well. FPL 12495 appeared to be more potent than remacemide in all its effects.

The effects of FPL 12495 are unusual in that no other investigated drug has yet shown a decrease in number together with an increase in mean duration of discharges. FPL 12495 appears to exert a differential action on the two commonly distinguished mechanisms controling number and duration.

Opioids and Spike-Wave Discharges in Rats: Pharmacological Studies. E. L. J. M. van Luijtelaar, *B. Przewlocka, *W. Lasón, *A. Coenen, and R. Przewlocki (Department of Psychology, University of Nijmegen, Nijmegen, The Netherlands; and *Institute of Pharmacology, Kraków, Poland).

Numerous studies have provided evidence for the involvement of opioids in the mechanisms of various forms of epilepsy. Most have investigated the effects of opioids in the control and genesis of convulsive epilepsy, whereas data on opioids mechanisms with respect to nonconvulsive epilepsy are almost lacking. Therefore, we investigated the role of the opioid subsystems in WAG/Rij rats, a genetic rat model of human absence epilepsy. Six-month-old male WAG/Rij were chronically provided with EEG electrodes and some with cannulas in the lateral ventricle. The baseline EEG was measured, and the drugs or solvent was injected. The EEG was recorded for 1 h, and the number and duration of spike-wave discharges (SWD) was counted.

SWD were facilitated by the nonspecific opioid antagonist naloxone (intraperitoneally), suggesting that SWD are tonically inhibited by the endogenous opioid system. Next, specific mu, delta and kappa agonists and antagonists were evaluated. The mu receptor agonist DAMGO increased (intracerebroventricularly, i.c.v.) markedly the number of SWD, whereas DPDPE, a delta receptor agonist, had no effect. Three kappa agonists (i.c.v. or subcutaneously) U50488H, U69593, or PD117301 dose-dependently inhibited the number of SWD. These effects could be antagonized by the kappa antagonist Nor-BNI. Nor-BNI itself enhanced the number of SWD, but the mu antagonist naltrindole had no effect.

Endogenous opioids, which act through the kappa receptors, tonically control the initiation of SWD. Kappa agonists, if devoid of psychomimetic effects, might be useful antiabsence drugs.

Effects of Tiagabine on Spike-Wave Discharges, Behavior, and Spectral Content of the EEG in Rats with Absence Epilepsy. A. M. L. Coenen, E. L. J. M. van Luijtelaar, and E. Blezer (Department of Psychology, University of Nijmegen, Nijmegen, The Netherlands).

The mechanism of action of the new anticonvulsant drug tiagabine (TGB) is reuptake inhibition of GABA. What TGB will do against nonconvulsive epilepsy is unclear. GABA agonists such as muscimol and anticonvulsants such as carbamazepine and phenytoin generally increase the number of spike-wave discharges (SWD). We wished to verify whether TGB would also facilitate the number of SWD in a genetic rat model for generalized absence epilepsy.

Male WAG/Rij rats with chronically implanted EEG electrodes were given either 0, 1, 3, or 10 mg/kg TGB intraperitoneally. The EEG was recorded for 1 h before and 2 h after drug administration. Behavior was recorded for 30 min postdrug; ambulation, passive behavior, and automatic behavior were scored.

TGB dose-dependently increased both the number and duration of SWD. The effect on the number lasted 75 min; the effect on SWD duration lasted slightly longer, ~1.5 h. TGB had no effects on behavior, and the effects on the background EEG were slight: Only the 25.3–39.0-Hz band was enhanced. The most striking finding was the occurrence of type 2 SWD (*Neurosci Lett* 1986;70:393–7), an occipital EEG transient. These brief (<2 s) SWD occurred only after administration of the two highest TGB doses. The mean number was 104 after 10 mg/kg TGB.

GABAergic drugs have opposite effects in convulsive and nonconvulsive epilepsy. The appearance of the brief type-2 SWD is unique for TGB. They deserve some attention, considering their large number and the fact that all rats at the highest dose showed these phenomena.

Febrile Hypothermia-Induced Seizures and Perspectives of Cognitive Functions Development: Experimental Study. N. E. Chepurnova, S. A. Chepurnov, *Jin-kyu Park, and Ki-youl Nam (Moscow State University, Moscow, Russia; and *Korea Ginseng & Tobacco Research Institute, Korea).

Clinicians have long been aware that infantile febrile convulsion (FC) affect seizure susceptibility and other neurological disorders (Volman, 1993). Severe FC can result in intellectual deterioration (*Epilepsia* 1971;11:187–97). Although a single (or series) induced FC may not be identical to a human FC, the susceptibility of infant rats (Sprague-Dawley, n = 90) to experimental seizures was investigated. The method of hypothermia-induced seizures of McCaugharan and Schechter (*Epilepsia* 1982;23:173–83) was used. The latency of FC, severity of convulsions, stereotypy, escape, running, and immobilization were identified in male and female rat pups. The infant rats were subjected to series of convulsions from age 5–15 days by hypothermia. In this experimental model of infantile FC, fraction V (diol and triol saponins and additional unknown compounds were mixed in a special ratio as a standard sample) and ginsenoside Rc from Korean red ginseng caused a long-lasting increase in susceptibility to the convulsant effects of pentylenetetrazol (PTZ) and a significant decrease in its effects in adulthood. Memory disturbances caused by hyperthermia after PTZ treatment were also improved by the same treatment.

Hippocampal Amygdala and Entorhinal Cortex Amino Acid Changes in Patients with Mesial Temporal Lobe Seizures. C. L. Wilson, N. T. Maidment, E. J. Behnke, I. Fried, and J. Engel, Jr. (UCLA Medical School, Los Angeles, CA, U.S.A.).

Candidates for temporal lobe surgery to relieve intractable seizures were evaluated preoperatively with chronically implanted intracranial EEG electrodes to determine areas of ictal onset (n = 10). Bilateral electrodes in amygdala, hippocampus, or entorhinal cortex carried microdialysis probes to sample extracellular amino acid (AA) changes in association with ictal and interictal EEG events. AA content in dialysate was determined by high-performance liquid chromatography with fluorimetric detection of OPA derivatives. Samples were taken every 30 min interictally and every 5 min after the onset of each seizure or during electrical stimulation.

The AA detected included cysteic acid, aspartate, glutamate, asparagine, serine, histidine, glutamine, glycine, citrulline, arginine, alanine, taurine, tyrosine, and GABA. During seizures, increases were repeatedly noted in aspartate, glutamate, citrulline, taurine, and GABA. Nontransmitter AA changes were absent or variable. Local electrical stimulation (0.2 Hz) delivered in a 10-min period produced two- to threefold increases in glutamate and GABA. These results support those of other laboratories showing AA release in association with seizure activity and also provide evidence for release during short periods of slow electrical stimulation. (Supported by NIH Grant No. NS02808.)

Effect of Theophylline on Glutamate and Aspartate Release from Rat Brain as Assessed by In Vivo Dialysis. Shigeru Nagaki, Yumiko Sakamoto, Makiko Osawa, *Noriko Mataga, *Fumihiko Fukamauchi, and †Nobumasa Kato (Department of Pediatrics, Tokyo Women's Medical College; *Medical Research Institute and Tokyo Medical and Dental University, Tokyo; and †Department of Psychiatry, Shiga Medical College, Shiga, Japan).

Although theophylline is a bronchodilator widely used in treating childhood bronchial asthma, we occasionally note theophylline-induced seizures that are difficult to control and may result in permanent neurologic damage or death. Although the mechanism is unclear, adenosine receptor antagonism by theophylline may contribute to seizure precipitation. Moreover, theophylline was recently reported to interact with *N*-methyl-D-aspartate (NMDA) receptors.

To elucidate further the mechanism of theophylline-induced seizures, we studied excitatory amino acid (AA: glutamate and aspartate) release in rat hippocampus and cerebrospinal fluid (CSF: cisterna magna), using microdialysis after acute theophylline administration (100 mg/kg intraperitoneally). Male Sprague-Dawley rats (300–400 g) were used. In rats under pentobarbital anesthesia, microdialysis probes (4 mm long, 200-μm diameter) were stereotaxically implanted in the hippocampus (5.6 mm posterior and 1.5 mm lateral to bregma, 8.2 mm ventral to surface) and cisterna magna. One day later, artificial CSF was infused through the probes at 2 μl/min. Dialysate samples (60 μl) were collected every 30 min for 6 h after theophylline administration and analyzed for amino acids by high-performance liquid chromatography.

Aspartate and glutamate concentrations were increased for 30 min after theophylline administration (140%), subsequently decreasing gradually (62%) for 4 h. Glutamate in hippocampal dialysate showed a tendency similar, though much weaker, to that in the CSF. Our results show that theophylline increased excitatory amino acid release from rat brain, possibly resulting in seizures.

FPL 12495AA and MK-801 Effects on Veratridine-Induced Glutamate Release. Jayashri Srinivasan, Alan Richens, and John A. Davies (University of Wales College of Medicine, Cardiff, U.K.).

FPL 12495AA, the desglycinated metabolite of remacemide, and MK-801 have an affinity for the ion channel subsite of the *N*-methyl-D-aspartate (NMDA) receptor and displace radiolabeled MK-801 (IC_{50} = 0.48 and 0.014 μ*M*, respectively). We compared the effects of FPL 12495AA and MK-801 on glutamate released from mouse cortex by veratridine (20 μ*M*) and assayed by high-performance liquid chromatography.

Basal release of glutamate was 3–5 pmol/mg tissue/2 min. The first pulse of veratridine induced an eight- to ninefold release of glutamate over basal value, and the second pulse produced a release that was 67 ± 6% of the first pulse. Release was significantly reduced by FPL 12495AA at concentrations of 12.5 μ*M* (39.3 ± 7.9%, $p < 0.05$, n = 4), 25 μ*M* (30.9 ± 9.4%, $p < 0.01$, n = 5), 50 μ*M* (29.4 ± 6.0%, $p < 0.01$, n = 5), 100 μ*M* (26.6 ± 6.2%, $p < 0.001$, n = 8), and 200 μ*M* (23.7 ± 6.7%, $p < 0.001$, n = 5). MK-801 reduced release in concentrations of 100 μ*M* (35.5 ± 2.8%, $p < 0.001$, n = 6) and 200 μ*M* (38.6 ± 7.2%, $p < 0.05$, n = 4); 50 μ*M* was ineffective.

MK-801 has 30 times greater affinity for the ion channel subsite of the NMDA receptor than FPL 12495AA. However, higher concentrations of MK-801 (100 μ*M*) are needed to reduce glutamate release as compared with FPL 12495AA (12.5 μ*M*). Therefore, FPL 12495AA probably acts by additional mechanisms; one possibility is that it inactivates sodium channels, a possibility supported by the observation that it inhibits sustained repetitive firing in neurons.