receptors, since adenosine agonists reduce epileptiform activity in some seizure models. The question that remains unanswered is the site of adenosine antiepileptic effect. Therefore, we wished to determine if the perirhinal cortex plays a role in the control of amygdaloid kindling. Male rats were surgically prepared under pentobarbital anesthesia. A tripolar electrode together with a guide cannula was stereotaxically implanted into right basolateral amygdala and perirhinal cortex, respectively. After postoperative recovery, animals were stimulated daily until five consecutive stage 5 seizures were observed. Microinfusion of 2-chloroadenosine (2-CLA 5, 10, and 100 n*M*) into perirhinal cortex of amygdala-kindled rats caused dose-dependent suppression of seizure activity. AD duration and stage 5 seizure duration was reduced, together with an increase for latency to stage 4 seizures. However, even at the highest dose (2-CLA 100 n*M*), no significant change in seizure stage was detectable. The effect of 2-CLA was long lasting (120 min), with the maximum effect observed 30 min after microinfusion of the drug. These results suggest that A1 adenosine receptors in the perirhinal cortex may play a role in modulating AD activity elicited from the amygdala. However, the relative importance of these receptors in suppressing behavioral seizure activity requires further evaluation.

Protective Effects of Peony Root Extract on Neuron Damage in the Cobalt Focus Epilepsy Model. T. Tsuda, A. Sugaya, H. Ooguchi, and *†E. Sugaya (Faculty of Pharmaceutical Sciences, Josai University; *Department of Physiology, Kanagawa Dental College; and †Institute for Oriental Medicine, Keio University, Japan).

We previously reported the antiepileptic action of peony root extract. This action involved inhibitory effects on pentylenetetrazol (PTZ)-induced bursting activity in snail neurons, inhibitory effects on PTZ-induced EEG power spectrum changes, inhibitory effects on sudden decrease in extracellular calcium associated with bursting activity, and inhibitory effects on intracellular calcium increase induced by PTZ. In the cobalt focus epilepsy model, not only severe spike discharge appeared in the EEG but severe neuron loss also was observed in the CA1 area of the hippocampus. To determine the detailed mechanism of antiepileptic action of peony root extract, we examined protective effects of peony root extract on neuron loss in the hippocampus.

When peony root extract was administered daily at a dose of 1 g/kg/day for 30 days before cobalt application, the neuron loss in the hippocampus induced by cobalt application was almost completely prevented. Administration at a dose of 0.5 g/kg/day also showed preventive effects, but the effects were less than those at a dose of 1 g/kg/day. These results suggest that peony root is a promising drug not only as an anticonvulsant but also as a protective agent against neuron damage associated with seizure activity.

Effect of Levetiracetam in a Genetic Model of Absence Epilepsy in Rats. A. J. Gower, *E. Hirsch, *A. Boehrer, M. Noyer, and *C. Marescaux (UCB Pharma Sector, Braine L'Alleud, Belgium; and *INSERM U398, C.H.U., Strasbourg, France).

Levetiracetam [ucb L059; (*S*)-α-ethyl-2-oxo-1-pyrrolidine acetamide] is a novel antiepileptic drug with a broad-spectrum anticonvulsant profile in animals (Gower et al., *Eur J Pharmacol* 1992;222:193–203) and promising early results in humans (Walker et al., Epilepsia 1994;35(suppl 7):76).

Levetiracetam was tested for its ability to block spontaneous EEG spike-wave discharges (SWD) in inbred, genetically susceptible rats. Rats of the GAERS strain (genetic absence epilepsy rat of Strasbourg) were injected with levetiracetam 5.4–170.0 mg/kg intraperitoneally, and the EEG was recorded from cortical electrodes continuously for 120 min. The duration of SWD, defined as 7–11 Hz, 200–1,000-μV amplitude, was measured directly from the EEG trace by visual inspection. Levetiracetam reduced SWD at all doses, on the average 70–85%. The already marked effects at the lowest dose precluded any clear dose–response relationship, although at the highest dose, 170 mg/kg, the onset time of effect was shorter and more animals reached >95% suppression. These results confirm previous findings in the PTZ model of absence epilepsy in rats and support a potential clinical application of levetiracetam in treating absence epilepsy, with effects likely at low doses.

Kinetics of Levetiracetam in Rat Blood and Cerebrospinal Fluid. Neville Ratnaraj, Helen C. Doheny, and Philip N. Patsalos (Department of Clinical Neurology, Institute of Neurology, London, U.K.).

Levetiracetam (ucb LO59) [(*S*)-α-ethyl-2-oxo-1-pyrrolidine acetamide], the enantiomer of the ethyl analogue of piracetam, is a centrally acting drug with potential therapeutic application in epilepsy. Its exact mechanism of action is unknown, but it probably acts indirectly on the GABA–benzodiazepine–chloride ionophore complex and the *N*-methyl-D-aspartate receptor. To elucidate further its mechanism of action, we first studied the kinetics of levetiracetam using a model that allows simultaneous sampling of blood (pharmacokinetics) and cerebrospinal fluid (CSF, neuropharmacokinetics) in freely behaving rats (Patsalos et al., *J Pharmacol Toxicol Methods* 1992;28:21–8).

Male Sprague-Dawley rats (250–300 g, n = 5) were administered 40 mg/kg levetiracetam intraperitoneally and CSF (30 μl) and blood (100 μl) was collected at intervals for 8 h and analyzed by high-performance liquid chromatography for levetiracetam content. The following pharmacokinetic and neuropharmacokinetic parameters, respectively, were obtained: T_{max} (min) 21.0 ± 3.7, 96.0 ± 6.0; C_{max} (μ*M*) 224.0 ± 23.7, 135.5 ± 13.8; area under the curve (μ*M*/h) 680.9 ± 68.1, 867.7 ± 61.7; and half-life (min) 113.8 ± 5.4, 304.8 ± 16.5. Levetiracetam readily enters the CSF compartment, but its efflux is significantly slower than that suggested by blood concentrations.

Block of the *N*-Methyl-D-Aspartate Receptor by Remacemide and Its *Des*-Glycine Metabolite. S. Subramaniam, S. D. Donevan, and M. A. Rogawski (Neuronal Excitability Section, Epilepsy Research Branch, NINDS, Bethesda, MD, U.S.A.).

Remacemide [(±)-2-amino-*N*-(1-methyl-1,2-diphenylethyl)acetamide], is a novel anticonvulsant currently undergoing clinical evaluation as add-on therapy for the treatment of generalized tonic-clonic and complex partial seizures. The precise molecular target mediating its therapeutic effect is not clear, although evidence suggests that it may act at the *N*-methyl-D-aspartate (NMDA) receptor. We characterized the effect of remacemide and its *des*-glycine metabolite on NMDA receptor currents in cultured rat hippocampal cells and on binding of [^{3}H]dizocilpine to rat forebrain membranes. Remacemide and *des*-glycine remacemide were selective blockers of NMDA receptor currents, but there were some differences in the blocking properties of the two drugs, suggesting that they act at distinct sites. *Des*-glycine remacemide was more potent than the parent (IC_{50} 2 vs. 80 μ*M*), and it exhibited enantioselectivity whereas remacemide did not. In addition, its blocking action occurred in a use- and voltage-dependent fashion, suggesting a channel-blocking mechanism. These results were supported by the findings in the [^{3}H]dizocilpine displacement experiments, except that the enantiomers of remacemide did show stereoselectivity. There was no evidence of a direct interaction between remacemide and the NMDA or glycine recognition sites. However, both the electrophysiological experiments and binding experiments were consistent with an interaction between remacemide and the facilitatory polyamine site on the NMDA receptor. Thus, remacemide and *des*-glycine remacemide have inhibitory actions through distinct sites on the NMDA receptor. However, during clinical use, only the *des*-