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recorded with sharp intracellular microelectrodes. This effect was accompanied by a reduction in the tonic repetitive firing induced by prolonged intracellular pulses. Both responses are mainly due to the activation of voltage-gated Na⁺ channels. In a different series of experiments, we used whole-cell, patch-clamp recordings in rat cerebellar granule cells in culture. In this preparation, TPM (200-500 μM, n = 6) induced a 15–22% reduction in the inward currents induced by depolarizing commands in the presence of K⁺ and Ca²⁺ channel blockers. This response was blocked by tetrodotoxin, indicating that it was presumably due to Na⁺ entry.

Our findings indicate that TPM can interact with voltage-gated Na⁺ electrogenesis in two types of rat central neurons. Such an effect may play a role in reducing the sustained firing of action potentials that accompany seizure activity and thus may represent an important mechanism of action for this drug.

**Cortical Disinhibition May Initiate the 3-Hz Spike-Wave Rhythm.** R. D. Deisz (MPI Psychiatry, Munich, Germany).

Absence epilepsies are characterized by generalized 3-Hz spike-wave discharges (SWD), the SWD rhythm, however, differs markedly from thalamic oscillations (Jahnsen and Llinás, J Physiol 1984; 349:227–47). We have further investigated paired-pulse depression (PPD) of inhibition (Deisz et al., NSL 1993; 154:209–12) using intracellular recordings from neocortical slices. PPD is due to activation of presynaptic γ-amino-butyric acid (GABA₁) receptors, causing reduced GABA release (Deisz and Prince J Physiol 1989; 412:513–41). PPD was examined at depolarized membrane potentials, yielding hyperpolarizing inhibitory postsynaptic potentials (IPSP) despite the overlap with excitatory PSP (EPSP). At stimulus intervals >400 ms, the second IPSP of a pair was reduced but was still hyperpolarizing. At intervals <300 ms, PPD reduced the IPSP much more, resulting in a net depolarization. Application of CGP 55845A antagonized PPD, i.e., restored the hyperpolarization of the second IPSP. Pharmacologically isolated IPSP (by CNQX and D-APV) exhibited a similar PPD. CGP 55845A reduced PPD of isolated IPSP to <10%, indicating that PPD is localized at GABAAergic interneurons. The reversal of the combined EPSP/IPSP from inhibition to excitation at 350 ms may determine the SWD rhythm through reentry excitation of the thalamus, closing the corticothalamic part of the loop. Alleviation of cortical PPD by GABAA antagonists may contribute to the beneficial effects of these drugs on absence epilepsies (Snead, Pharmacol Commun 1992; 2:63–9).

**Reduced Effect of Carbamazepine on Sodium Currents in Epileptogenic Brain Areas of Pharmacoresistant Patients.** M. Veugenhenhi, F. H. Lopes da Silva, and W. J. Wadman (Amsterdam, The Netherlands).

The effect of carbamazepine (CBZ: 15, 40, and 100 μM) on whole-cell sodium current (INa) was studied in cells enzymatically isolated from tissue resected from pharmacoresistant patients. We compared different areas (hippocampal CA1 and neocortex) and different pathologies [mesiotemporal sclerosis CAS and NCS from the same patients] versus tumor-associated epilepsies with a mesiolimbic tumor (CAT) or neocortical tumor (NCT).

Voltage steps positive to −55 mV evoked voltage-dependent INa. Maximal conductance was 100 nS for CAS, 153 nS for CAT, 89 nS for NCS, and 72 nS for NCT and was not affected by CBZ. Half-maximal activation potential was −30 mV for all groups and was not affected by CBZ. INa inactivation at −20 mV had a time constant of 1.6 ms for all groups and was faster with CBZ. The half-maximal inactivation potential (V½) was −66 mV for CAS, −65 mV for CAT, −62 mV for NCS, and −63 mV for NCT. CBZ shifted the V½ to a more hyperpolarized level. The mean dose–response relation was fit for a maximal shift of −28 mV with a Kᵣ of 113 μM in CAS, 63 μM in CAT, 57 μM in NCS, and 155 μM in NCT. Recovery from inactivation at −80 mV had a time constant of 12 ms for all groups and was 30% slower with 100 μM CBZ.

INa was relatively large in CA1 neurons from tumor-associated epilepsies as compared with sclerosis. The effect of CBZ on INa was reduced in neurons obtained from CAS and NCT as compared with NCS and NCT.

**The Hill Parameter Depends on γ-Aminobutyric Acid (GABA): An Explanation for Individual Responses to GABA Mimetics?** Clementina M. van Rijn, Ris Dirksen, and Elly Willems (Departments of Psychology/NICI and Anaesthesiology, University of Nijmegen, The Netherlands).

The interest of epileptologists in GABA mimetics is due to the potent anticonvulsive effects of these drugs. The molecular mechanisms of compounds interacting with the GABAA receptor complex are not yet fully understood, however. Therefore, we investigated the effects of thiopental and propofol, either with or without GABA, in receptor binding studies to rat brain membranes.

Both compounds displaced [³H]t-buty1bicycloothoacetanate ([³H]TBOB) binding to the GABAA receptor complex. The data were fitted to the sigmoid Emax model (Hill equation). Both the EC₅₀ value and the Hill parameter (slope factor) were dependent on the GABA concentration: Addition of 8 μM GABA decreased the EC₅₀ of thiopental from 100 to 15 μM and that of propofol from 40 to 5 μM. The Hill parameter of thiopental decreased from 2.2 to 1.4 and that of propofol decreased from 2.4 to 0.9.

The sigmoid Emax model does not correspond to a molecular model. We present a molecular model that may explain the results and describes the influence of the GABA binding site on the cooperation between two binding sites for thiopental or two sites for propofol. These in vitro studies show that the shape of the dose–response curve of a drug may depend on the copresence of other compounds, which may explain inter- and intraindividual differences in responses to psychopharmacology including antiepileptic drugs.

**AWD 140-190 Exerts Anticonvulsant Activity in Hippocampal Slice Preparations.** V. Armando, U. Heimann, *R*. Dost, and *C*. Rundfeldt (Department of Neurophysiology, Charité, Berlin; and *Department of Pharmacology, Corporate R&D, ASTA Medica Group, Arzneimitteiherk Dresden, Radebeul, Germany).

AWD 140-190 (4-(4-bromophenyl)-3-morpholino-pyrrole-2-carboxylic acid methyl ester) is one of the most potent anticonvulsants selected from a series of 150 3-aminopyrroles, in primary screening. The drug is effective against electrically but not against metrazol-induced convulsions. It exerts potent effects in a predictive model for complex partial seizures: amygdala kindling in rats (Rostock et al., Soc Neurosci Abstr 1995; 24). For further characterization, AWD 140-190 was tested in two in vitro models of epileptic discharge, i.e., the low calcium and the low magnesium models, and in the paired pulse facilitation paradigm in the combined hippocampal and entorhinal cortex slice preparation.

In the low magnesium model, the drug reduced the frequency of short recurrent discharges in area CA1 only after application of 200 μM, the highest concentration tested. Evaluation of the effect of AWD 140-190 on the pharmacoresistant late phase of discharge showed the activity to be similar to that of phenytoin. In the low calcium model, the epileptiform activity was fully suppressed by 20-min bath application of 12.5 μM after 120 min. An increase in concentration to 25 and 100 μM reduced the time for full suppression to 51 and 33 min, respectively.

The frequency-dependent facilitation of neuronal activity in CA1 region evoked by stimulation of the Schaffer collaterals with paired pulses was reduced by AWD 140-190 (25 and 50 μM). The effect was most pronounced at high stimulation frequencies. The dose-dependent activity of AWD 140-190 in the low calcium model

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