The Johns Hopkins Series
in Contemporary Medicine
and Public Health

ALSO OF INTEREST IN THIS SERIES:

Neuropeptides in Psychiatric and Neurological Disorders,
edited by Charles B. Nemeroff, M.D., Ph.D.

Problems and Concepts in Developmental Neurophysiology

EDITED BY

Peter Kellaway, Ph.D., and
Jeffrey L. Noebels, M.D., Ph.D.

Section of Neurophysiology
Department of Neurology
Baylor College of Medicine

THE JOHNS HOPKINS
UNIVERSITY PRESS
Baltimore and London

Printed in the United States of America

The Johns Hopkins University Press, 701 West 40th Street, Baltimore, Maryland 21211
The Johns Hopkins Press Ltd., London

The paper used in this publication meets the minimum requirements of American National Standard for Information Sciences—Permanence of Paper for Printed Library Materials, ANSI Z39.48-1984.

Library of Congress Cataloging-in-Publication Data

Problems and concepts in developmental neurophysiology.
(The Johns Hopkins series in contemporary medicine and public health)
Based on a symposium held in Houston, Tex., in 1984.
Includes index.
1. Developmental neurophysiology—Congresses. I. Kellaway, Peter, 1920– .
II. Noebels, Jeffrey L. III. Series. [DNLM: 1. Brain—growth—congresses.
2. Brain—physiology—congresses. 3. Electrophysiology—
congresses. WL 300 P9616 1984]
QP356.25.P76 1989 612'.64018 88-46069
ISBN 0-8018-3790-1 (alk. paper)

CONTENTS

List of Contributors vii
Preface ix
Acknowledgments xi

I. Plasticity and Sensitive Periods

1. Introduction to Plasticity and Sensitive Periods, PETER KELLAWAY 3
2. The Developmental Neurogenetics of Spike-and-Wave Epilepsy, JEFFREY L. NOEBELS 29
3. Sensitive Periods in Visual Development in the Kitten: The Effects of Early Monocular Deprivation, DONALD E. MITCHELL 45
4. Experimental Amblyopia Ex Anopsia in the Kitten: A Neuropharmacologic Approach, TAKUJI KASAMATSU 75
5. Noradrenergic Modulation of Synaptic Plasticity in the Hippocampus, WILLIAM F. HOPKINS AND DANIEL JOHNSTON 92
6. Evidence for a Possible Role of Spontaneous Electrical Activity in the Development of the Mammalian Visual Cortex, MICHAEL P. STRYKER 110
7. Infantile Spasms: A Disorder of the Developing Nervous System, RICHARD A. HRACHOVY AND JAMES D. FROST, JR. 131

II. Structure-Function Relationships in the Developing Brain

8. Introduction to Structure-Function Relationships in the Developing Brain, JEFFREY L. NOEBELS 151
9. Neurophysiologic Development in Primary Cell Cultures, MEYER B. JACKSON, PAULA LEVEILLE, ROBIN S. FISHER, AND LINDA ATTARDO 161

10. The Biochemical Development of GABA Transmission, EUGENE M. BARNES, JR. 186

11. Electrophysiologic Studies of Immature Neocortical Neurons, DAVID A. PRINCE AND ARNOLD R. KRIEGSTEIN 198

12. Cellular Properties of Convulsant-Treated Neocortical Neurons in the Rat during Postnatal Development, JOHN J. HABLITZ AND BERND SUTOR 212

13. The Developmental Electrophysiology of the Rabbit Hippocampus, PHILIP A. SCHWARTZKROIN, DENNIS D. KÜNKEL, ALAN L. MUELLER, AND MICHAEL M. HAGLUND 225

14. The Ontogeny of Seizures and Substantia Nigra Modulation, SOLOMON L. MOSHÉ 247

15. Electrophysiologic Indices of Normal and Aberrant Cortical Maturation, HERBERT G. VAUGHAN, JR., AND DIANE KURTZBERG 263

Index 289

CONTRIBUTORS

LINDA ATTARDO, staff research associate, Department of Biology, Mental Retardation Research Center, University of California, Los Angeles

EUGENE M. BARNES, Jr., Ph.D., professor, Department of Biochemistry, Department of Physiology and Molecular Biophysics, and Program in Neuroscience, Baylor College of Medicine

ROBIN S. FISHER, Ph.D., assistant professor, Department of Anatomy, Mental Retardation Research Center, University of California, Los Angeles

JAMES D. FROST, Jr., M.D., professor, Section of Neurophysiology, Department of Neurology, Baylor College of Medicine

JOHN J. HABLITZ, Ph.D., associate professor, Section of Neurophysiology, Department of Neurology, and Department of Physiology and Molecular Biophysics, Baylor College of Medicine

MICHAEL M. HAGLUND, M.D., resident, Department of Neurological Surgery, University of Washington

WILLIAM F. HOPKINS, Ph.D., assistant professor, Department of Neurology, Oregon Health Sciences University

RICHARD A. HRACHOVY, M.D., associate professor, Section of Neurophysiology, Department of Neurology, Baylor College of Medicine

MEYER B. JACKSON, Ph.D., associate professor, Department of Biology, Mental Retardation Research Center, University of California, Los Angeles

DANIEL JOHNSTON, Ph.D., professor, Section of Neurophysiology, Program in Neuroscience, Department of Neurology, and Department of Physiology and Molecular Biophysics, Baylor College of Medicine

TAKUJI KASAMATSU, M.D., senior scientist, Smith-Kettlewell Institute of Visual Sciences, San Francisco

ARNOLD R. KRIEGSTEIN, M.D., Ph.D., assistant professor, Department of Neurology, Stanford University School of Medicine

DENNIS D. KÜNKEL, Ph.D., research associate, Department of Neurological Surgery, University of Washington

DIANE KURTZBERG, M.D., associate professor, Department of Neuroscience and Neurology, Albert Einstein College of Medicine

PAULA LEVEILLE, research anatomist, Department of Anatomy, Mental Retardation Research Center, University of California, Los Angeles

DONALD E. MITCHELL, Ph.D., professor, Department of Psychology, Dalhousie University

SOLOMON L. MOSHÉ, M.D., associate professor, Department of Neurology and Department of Pediatrics, Albert Einstein College of Medicine

ALAN L. MUELLER, Ph.D., Abbott Laboratories, Abbott Park, Illinois

DAVID A. PRINCE, M.D., Edward F. and Irene Thiele Pimley Professor of Neurology and Neurological Sciences and Chairman, Department of Neurology, Stanford University School of Medicine

PHILIP A. SCHWARTZKROIN, Ph.D., professor, Department of Neurological Surgery and Department of Physiology and Biophysics, University of Washington

MICHAEL P. STRYKER, Ph.D., professor, Department of Physiology, University of California School of Medicine, San Francisco

BERND SUTOR, Ph.D., fellow, Section of Neurophysiology, Department of Neurology, Baylor College of Medicine

HERBERT G. VAUGHAN, Jr., M.D., professor, Department of Neuroscience and Neurology and Department of Pediatrics, and director, Rose F. Kennedy Center for Research in Mental Retardation and Human Development, Albert Einstein College of Medicine

CHAPTER TWELVE

Cellular Properties of Convulsant-Treated Neocortical Neurons in the Rat during Postnatal Development

John J. Hablitz and Bernd Sutor

Postnatal development of the neocortex has been described in numerous anatomic studies. The increases in somatic volume, dendritic arbor, and spine complexes that occur in the first few postnatal weeks have been documented by Golgi staining techniques (8,24,25), and information about the maturation of synaptic elements has been provided by electron microscopy (15,25,40). However, cellular interactions and neuronal integration have not been studied extensively in the immature rat brain. Electrophysiologic studies, using intracellular injection of the fluorescent dye Lucifer Yellow, have shown that dye coupling, thought to be an indicator of electrotonic coupling, is extensive in immature rat neocortex and declines rapidly between birth and 10 days of age (5). Developmental studies of cerebellar nuclear cells (9) and rabbit hippocampal pyramidal neurons (28,29) indicate that most intrinsic membrane conductances mature within the first postnatal week. Inhibitory and excitatory postsynaptic potentials have been observed in intracerebellar nuclei neurons on the second postnatal day (9). Despite these indications that basic cellular and synaptic responses are established early, distinct differences in patterns of epileptiform discharge exist between the immature and mature brain. Recordings of paroxysmal activity from epileptogenic foci in the immature brain in vivo have shown that synaptic potentials and interictal spike discharges last longer and are more variable in size than those recorded from similar foci in the mature brain (26). Foci in the developing brain have a lower rate of spontaneous discharge (2), and seizure episodes, which are prominent in the mature brain (22), are not typically observed in the developing cortex (11). Recent experiments on hippocampal slices prepared from neonatal animals (28,35) have shown that there is

a seizure-prone period between postnatal days 9 and 19. In the present study, we examined the response of neocortical slices from rats 8–21 days old to convulsant drugs to determine whether there was a significant age-dependent variation in the pattern of epileptiform discharge. We also characterized the membrane properties of neurons in this age range.

Neocortical slices were prepared using standard techniques (34,41) and were maintained in an interface type of chamber. Slices were allowed to recover for a period of 1 hr prior to the addition of 50 μM picrotoxin to the perfusate. Intracellular recordings were made from superficial strata (layers II–IV) of anterior somatosensory cortex.

Cellular Properties of Immature Neurons

The neurons in slices from immature animals had an average resting membrane potential (RMP) of -66 ± 4 mV (N = 33) and an input resistance (R_N) of 38 ± 21 MΩ (N = 33). The value for the RMP was lower than that obtained from mature animals (-76 ± 8 mV, N = 113), but the difference was not statistically significant. R_N tended to be larger in immature than in mature neurons ($R_N = 20 \pm 7$ MΩ, N = 95), but the great variability in seemingly good impalements of neonatal neurons makes this difference difficult to evaluate. Action potential duration (measured at half-maximal amplitude) was longer in neurons from immature animals (1.9 ± 1.4 msec, N = 26 vs. 0.8 ± 0.2 msec, N = 95 for the mature group). This did not seem to be due to impalement injury, since there was no correlation between spike height and membrane potential. Broad, overshooting spikes were observed in neurons with stable, high resting potentials and high input resistances.

Neocortical neurons in vivo (4) and in vitro (23,32) are known to fire repetitively in response to depolarizing current pulses and to show adaptation during long current pulses. As shown in fig. 12.1A, similar behavior was observed in neurons from immature rat cortex. Individual action potentials were followed by an afterhyperpolarization (AHP). This AHP, which was very pronounced in immature neurons, became deeper with succeeding spikes and appeared to mediate the observed adaptation. Typically, trains of action potentials were followed by a short, rapid AHP and a more slowly decaying, long-lasting AHP. These slow AHPs, similar to those described by Connors et al. (5), were 2–5 mV in amplitude and lasted as long as 900 msec.

When hyperpolarizing current pulses were applied, distinct differences were observed between neurons from immature and adult animals. Results suggested that neurons could be grouped into two broad categories, namely <16 days of age and >16 days of age. Neurons from animals <16 days of age typically showed the type of behavior illustrated in fig. 12.1B. A marked, time-dependent inward rectification was noted with hyperpolarizing current pulses. This appeared as a sag in the voltage records (fig. 12.1B) that began 5–20 msec after

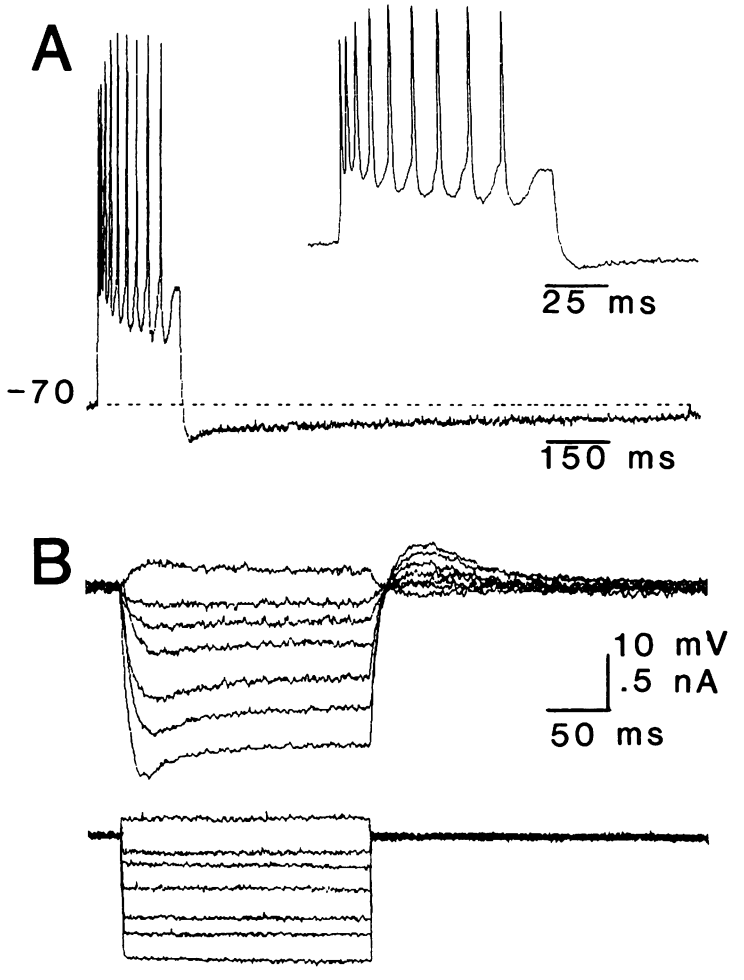

Fig. 12.1. Response of a neuron from a 10-day-old animal to hyperpolarizing and depolarizing current pulses. A: Example of repetitive firing and afterhyperpolarization (AHP) produced by a strong depolarizing current pulse. Inset shows action potentials at a higher sweep speed. B: Superimposed voltage responses (upper traces) to current pulses of varying amplitude (lower traces). Hyperpolarizing pulses produce responses that reach a peak and then sag to a steady-state level. Rebound depolarizations are seen at pulse offset. Same cell and resting potential (RMP) as in A.

the onset of the current pulse and reached a steady state in 40–90 msec. Some sag was observed with hyperpolarizing currents that caused membrane potential changes of 10 mV, suggesting that the current underlying this response was activated at values near rest. This type of behavior was seen in more than 80 percent of the neurons in the <16-days-of-age group. Sagging was less preva-

lent in the older animals, although it was occasionally observed in neurons from mature cortex.

Another prominent feature of the response of neocortical neurons to hyperpolarizing current pulses in the <16-days-of-age group was the rebound depolarization observed at pulse offset. This response was graded (fig. 12.1B) and could exceed threshold for spike initiation. Depolarizations associated with pulse offset were seen in 60 percent of the cells in the <16-days-of-age group. Two pieces of evidence suggested that this depolarization was a separate process from the one responsible for the hyperpolarizing sag. First, some cells with prominent sags did not show anodal break depolarizations, and second, alterations in membrane potential had differential effects on the two responses.

The rebound depolarization observed here has also been described in cerebellar nuclear cells (14). In those cells, repetitive spiking was observed when large-amplitude current pulses were used. In our experiments, rebound spiking was rare when pulses were applied with the cell held at its resting membrane potential, although one or occasionally two action potentials were seen at the offset of the pulse. However, the amplitude of the rebound depolarization and the number of resulting action potentials could be altered by manipulating the membrane potential with steady currents. A particularly dramatic example is shown in fig. 12.2. A subthreshold rebound depolarization was seen when a

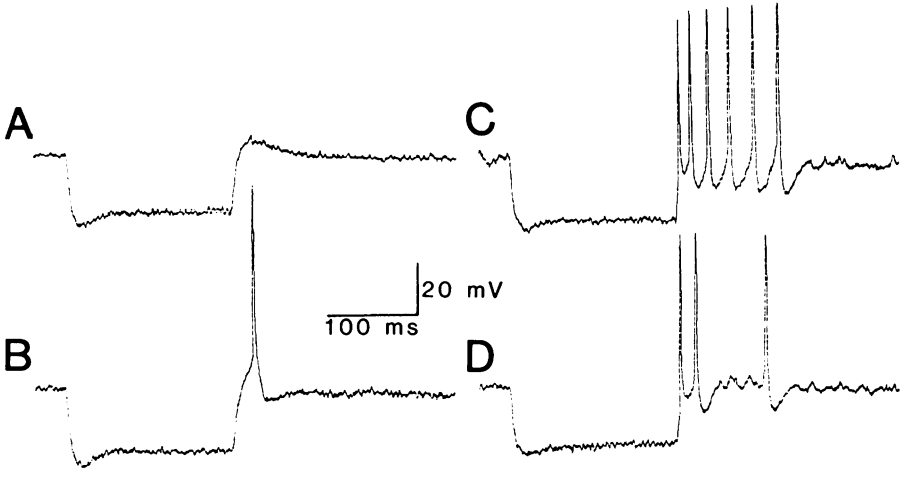

Fig. 12.2. Effect of alterations in membrane potential on rebound depolarization. A: Subthreshold depolarization occurs at pulse offset in the absence of applied steady current (RMP = −65 mV). B: Single action potential is evoked when cell is depolarized by 5 mV. C: Train of action potentials occurs with depolarization to −55 mV. D: The R_N and the number of rebound discharges decrease as the cell is depolarized further to −50 mV. A hyperpolarizing current pulse of 0.6 nA was used in all traces.

hyperpolarizing current step was applied at the resting potential (fig. 12.2A). When the cell was depolarized, the same current pulse produced a rebound depolarization that triggered an action potential (fig. 12.2B). Further depolarization resulted in the elicitation of a train of action potentials (fig. 12.2C), although the hyperpolarizing sag was no longer observed. A decrease in R_N and in the number of rebound action potentials was observed with additional depolarization (fig. 12.2D). Such pronounced rebound depolarizations were never observed in neurons from adult animals.

Convulsant-Induced Epileptiform Activity in Mature and Immature Neocortex

Convulsant-treated neocortical slices from mature guinea pigs display epileptiform activity consisting of large depolarizations that trigger bursts of fast action potentials (10). These paroxysmal depolarizing shifts (PDSs) were stereotyped, although the latency to onset varied with the stimulus strength. We have made similar observations in mature rat neocortical neurons. Figure 12.3

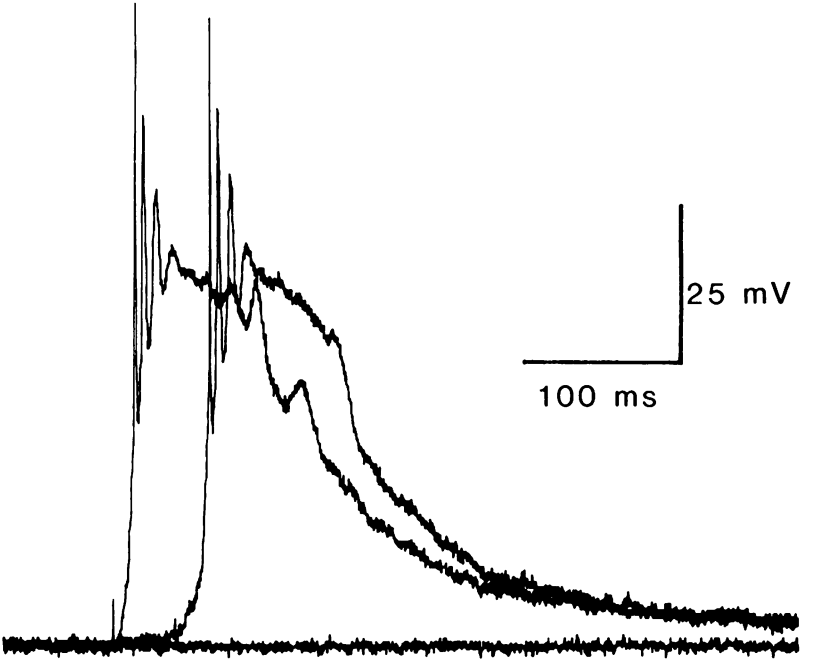

Fig. 12.3. Examples of synaptically evoked PDSs in a neocortical neuron from an adult rat. Responses were evoked 15 min after starting perfusion with a saline containing 10 μM bicuculline. Three stimuli of increasing strength were applied. The charges delivered to the stimulating electrode were 3.75, 5.0, and 6.25 nC. The resting membrane potential of this cell was −78 mV.

shows the neuron's response to three intracortical stimuli of increasing intensity. The first stimulus was below threshold and did not evoke a detectable response. The second stimulus evoked an excitatory postsynaptic potential that led to a PDS at a latency of 19 msec. Further increases in the strength of stimulation evoked a PDS that rose rapidly from the baseline after a delay of 4 msec. In agreement with the report of Gutnick et al. (10), no spontaneous epileptiform activity was observed in neocortical slices from mature animals.

In contrast to slices from mature animals, two patterns of spontaneous epileptiform activity were observed in convulsant-treated slices from immature brain. Similar activity could be triggered by a single shock applied intracortically or to the pial surface. The first pattern was seen in slices from 8- to 15-day-old rats and consisted, in extracellular recordings, of paroxysms of repetitive spike discharges superimposed on a 3- to 5-mV, slow negative potential. Spontaneous paroxysms were 10–30 sec in duration, and the intervals between these events varied from 30 to 180 sec in different preparations. Similar episodes could be evoked by electrical stimulation of intracortical fibers, the pial surface, or the subjacent white matter. Intracellular recordings showed that each paroxysm was accompanied by a membrane depolarization and sustained firing. Examples of such activity from two neurons are shown in fig. 12.4. A single stimulus was used to evoke the discharge shown in fig. 12.4A; the responses in fig. 12.4B occurred spontaneously. The observed depolarization was associated with an increase in conductance, as indicated by the decreased voltage transient in response to a constant-current hyperpolariz-

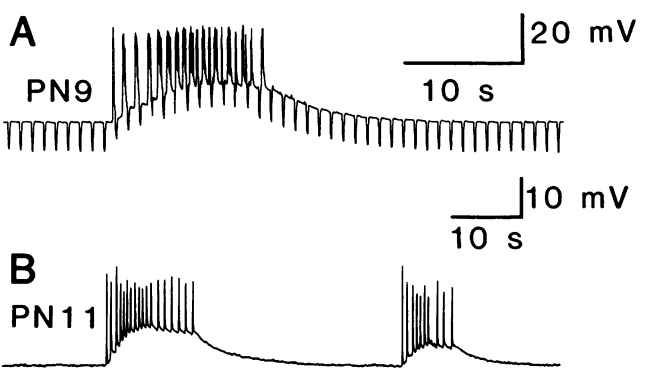

Fig. 12.4. Intracellular recordings of epileptiform responses in the <16-day group. A: Recording from a neuron from a 9-day-old rat (PN9). A single orthodromic stimulus triggered the response shown. The negative deflections are the voltage responses to 150-msec, 0.4-nA hyperpolarizing current pulses. RMP was −62 mV. B: Spontaneous epileptiform events recorded in a postnatal day 11 (PN11) neuron. RMP was −62 mV. Chart recorder tracings are shown in A and B; full height of action potentials is not shown.

ing step (fig. 12.4A). It should be noted that the paroxysmal bursts were not followed by an AHP.

The second pattern of spontaneous epileptiform activity was seen in convulsant-treated slices from animals 16–21 days old. Extracellular recordings showed paroxysmal activity consisting of 3–10 spike discharges followed by a sustained, slow, negative-potential shift. This slow potential could last as long as 180 sec and could reach amplitudes of up to 30 mV. Paroxysmal events recurred spontaneously at intervals of 4–11 min, over periods of hours. Spontaneous PDSs and slow, negative-potential shifts were not observed in picrotoxin-treated slices from animals over 30 days of age, although PDSs could still be evoked by stimulation.

Intracellular recordings in the 16- to 21-day group revealed that each paroxysmal event began with a membrane depolarization similar to that observed in the <16-day group. Examples from two neurons are shown in fig. 12.5. Such depolarizations (onset indicated by the single arrow in fig. 12.5A and B) were associated with bursts of repetitive action potentials. This was followed, at a varying latency, by a large, sustained membrane depolarization (fig. 12.5A and B, double arrow). This depolarization, termed a long-lasting depolarization (LLD) slowly declined and was followed, in fig. 12.5A, by an AHP. Fig. 12.5B shows a similar pattern, except that the LLD is followed by an afterdepolarization. Complete recovery of baseline values for resting potential and R_N was achieved after several minutes. The downward deflections in fig. 12.5 represent the voltage displacement in response to hyperpolarizing current pulses and monitor neuronal R_N. It can be seen that the paroxysmal event was associated with a complicated series of changes in R_N. Decreases in R_N occurred during the initial depolarization, which only partially recovered prior to

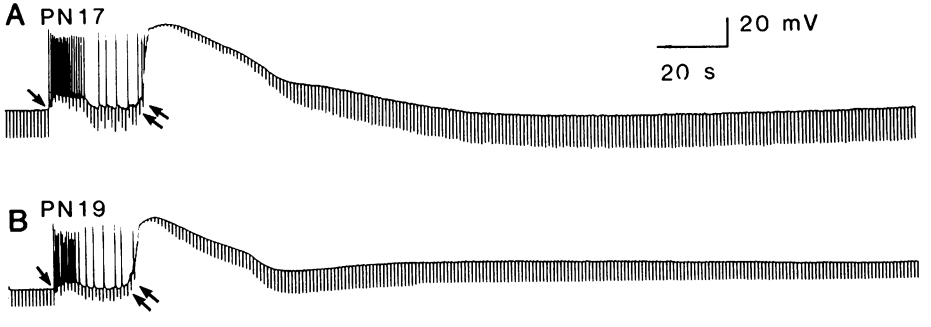

Fig. 12.5. Specimen records of spontaneous epileptiform discharges in the 16- to 21-day-old group. A: Chart-recorder tracings of a burst of PDSs (single arrow) followed by a long-lasting depolarization (double arrow) in a postnatal day 17 (PN17) neuron. Downward deflections are voltage responses to a 0.3-nA hyperpolarizing current pulse. RMP was −82 mV. B: Similar recording, but from a postnatal day 19 (PN19) neuron. Current pulse, 0.3 nA; RMP, −63 mV.

the onset of the LLD. During the peak of the LLD, R_N was virtually immeasurable, indicating a large conductance increase. R_N recovered slowly over time as the LLD declined but then apparently increased over control values during the afterpotentials. However, in other neurons, LLDs were followed by an AHP associated with a decrease in R_N. The significance of these changes in R_N during the afterpotentials is unclear, however, since adequate electrode compensation was difficult to maintain during and immediately after the LLD; this probably resulted from the changes in extracellular resistivity associated with the shrinkage of the extracellular space that occurred during LLDs (13).

Extracellular Potassium Changes during Epileptiform Activity in Immature Neocortex

It has been reported that the increases in extracellular potassium ($[K^+]_o$) that occur during epileptiform discharges are enhanced in the immature hippocampus (35). To determine whether similar changes occur in the immature neocortex, ion-sensitive electrodes were used to measure changes in $[K^+]_o$. These studies were conducted in collaboration with Dr. Uwe Heinemann, at the Department of Neurophysiology, Max-Planck Institute for Psychiatry, Martinsried FRG. The results of experiments in the <16-day group are shown in fig. 12.6A. It can be seen that $[K^+]_o$ rapidly increases to more than 20 mM during paroxysmal activity and slowly declines after the epileptiform activity ceases. In contrast, in the >16-day group (fig. 12.6B), $[K^+]_o$ rises to over 10 mM during epileptiform activity and then abruptly increases again during the slow potential associated with the onset of the LLD. A pronounced undershoot of $[K^+]_o$ follows, after which there is a return to baseline $[K^+]_o$ levels over a period of minutes. $[K^+]_o$ is then stable until the onset of the next paroxysmal event, when the sequence described above is repeated.

Conclusions

These results demonstrate that several unique types of epileptiform activity occur in neocortical slices from immature rats. Each type of activity occurs preferentially within a restricted time frame and is not seen before slices are exposed to convulsants. Because of its spontaneous nature and long duration, paroxysmal activity in vitro in immature neocortex differs phenomenologically from that observed in slices from mature brain. These characteristics suggest that paroxysmal activity in the immature animal may be a useful model for the study of ictal seizure discharges and perhaps the transition from interictal to ictal discharge.

It is now generally agreed that several factors contribute to the generation of epileptiform discharges. Alterations in the extracellular microenvironment (20,27), electrical coupling (21), endogenous membrane currents (42), and

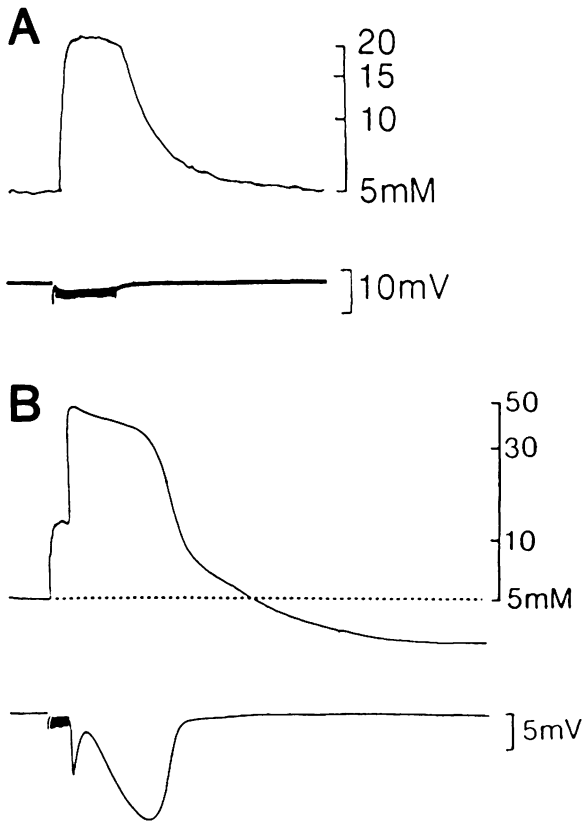

Fig. 12.6. Changes in $[K^+]_o$ associated with epileptiform discharges in the immature rat neocortex. A: Specimen record of $[K^+]_o$ changes (upper trace) during epileptiform activity (lower trace) in a slice from a 12-day-old rat. Recordings were made 600 μm below the pial surface. B: Similar experiment in a slice from a 19-day-old rat. These recordings were made 750 μm below the pial surface.

synaptically evoked depolarizations (1,12,16) all add to the PDS that accompanies abnormal activity. The relative contribution from each factor is likely to vary according to the type of epileptiform activity expressed, the brain region involved, and the stage of development. The present results indicate that the immature cortex may differ significantly from the adult cortex in certain intrinsic membrane currents and in changes in the extracellular microenvironment induced by epileptiform discharge.

In the present studies, immature neurons had broad action potentials, displayed marked time-dependent inward rectification that was not prevalent in mature rat neocortical neurons (6,41), and frequently showed rebound depolarizations at the offset of hyperpolarizing pulses. All of these factors could

lead to the increased excitability observed after exposure to convulsant drugs. The broader spikes in neurons from immature animals could, if propagated into synaptic terminals, produce increased transmitter release, leading to greater excitation. Hyperpolarizing inward rectification could, in principle, reduce the effectiveness of hyperpolarizing influences that normally curtail epileptiform discharges (31). Our findings suggest that the rebound depolarization results from activation of a voltage-dependent current. Persistent sodium and calcium currents have been described in neocortical neurons (33), and such currents could contribute to the rebound depolarizations. On the other hand, it is not possible to rule out a mechanism involving a low-threshold calcium current deinactivated by the hyperpolarizing pulse (18). Regardless of its ionic nature, the current underlying the rebound depolarization would enhance neuronal excitability and might contribute to the propensity of immature neocortex to display prolonged epileptiform discharges. More detailed studies are needed to determine whether quantitative differences exist between immature and mature cells with regard to the magnitude and voltage dependence of intrinsic membrane currents.

Another important feature distinguishing immature from mature neocortex is the changes in the extracellular microenvironment that accompany epileptiform discharges. Using ion-sensitive electrodes, we have shown that epileptiform discharges in the immature neocortex are associated with unusually high levels of $[K^+]_o$ (13). The cause of the higher levels of $[K^+]_o$ associated with repetitive firing in the early postnatal period is presently unclear. However, similar results have been obtained in the hippocampus (36), which suggests that an elevated ceiling for $[K^+]_o$ may be a general property of the neonatal period. The sustained increases in $[K^+]_o$ that were observed could heighten neuronal excitability by several mechanisms, e.g., by a direct depolarizing action, by release of excitatory neurotransmitters, or by reducing the effectiveness of repolarizing potassium currents. Elevation of $[K^+]_o$ may thus be involved in the maintenance of the prolonged ictal-like epileptiform activity observed in the immature neocortex.

The levels of $[K^+]_o$ associated with the LLDs observed in the 16- to 21-day-old animals indicate that they represent a type of spreading depression (SD). This interpretation is supported by our observation of a conduction velocity of approximately 4 mm/min for LLDs. SD is a transient pathologic state associated with large changes in intra- and extracellular ion concentrations and movement of water (17). The relationship between SD and epileptiform activity has been examined by numerous investigators. SD has been reported to elicit epileptiform activity (39) as well as to suppress it (30). Paroxysmal discharges can, in turn, both trigger (38) and block (3,37) SD. In the present study, there was a unique relationship between epileptiform activity and SD-like LLDs. A burst of epileptiform discharges would arise from a quiet background and apparently trigger an LLD. A latency of tens of seconds could be observed

between the initiation of burst discharges and the onset of an LLD, suggesting that the SD underlying the LLD was triggered remotely and slowly propagated to the recording site. The present results suggest that different mechanisms are involved in the generation of paroxysmal burst discharges and LLDs. The former were similar in the <16-day group and the 16- to 21-day animals; yet LLDs were observed only in the latter group. Moreover, laminar profiles demonstrated that paroxysmal burst discharges reversed in polarity in deeper cortical layers, whereas the slow potential shifts associated with LLDs did not. Such laminar profiles would be consistent with a neuronal origin for the former but not the latter (7,19). Apparently, during the 16- to 21-day postnatal period studied here, the rat neocortex is susceptible to the triggering of SD by epileptiform discharges. The factors responsible for this have not been determined, but the occurrence of spontaneous recurrent episodes of SD provides a useful model system for study of the SD phenomenon.

In summary, we have shown that neocortical slices from immature rats display several novel patterns of ictal-like epileptiform discharges. Differences in intrinsic membrane currents and $[K^+]_o$ regulation seem to be responsible, at least in part, for the differences observed in the neonatal period. Studies of developmental differences in synaptic potentials are currently being conducted to determine the role of this factor in epileptogenesis in the immature brain.

Acknowledgments

This work was supported in part by NIH grants NS11535 and NS22373. B. Sutor was the recipient of a Max Kade Foundation Fellowship.

References

1. Ayala, G.F., Matsumoto, H., and Gumnit, R.J. (1970): Excitability changes and inhibitory mechanisms in neocortical neurons during seizures. *J. Neurophysiol.* 33:73–85.
2. Bishop, E.J. (1950): The strychnine spike as a physiological indicator of cortical maturity in the postnatal rabbit. *Electroencephalogr. Clin. Neurophysiol.* 2:309–315.
3. Bureš, J., von Schwarzenfeld, I., and Brožek, G. (1975): Blockage of cortical spreading depression by picrotoxin foci of paroxysmal activity. *Epilepsia* 16:111–118.
4. Calvin, W.H., and Sypert, G. W. (1976): Fast and slow pyramidal tract neurons: an intracellular analysis of their contrasting repetitive firing properties in the cat. *J. Neurophysiol.* 39:420–434.
5. Connors, B.W., Benardo, L.S., and Prince, D.A. (1983): Coupling between neurons of the developing rat neocortex. *J. Neurosci.* 3:773–782.
6. Connors, B.W., Gutnick, M.J., and Prince, D.A. (1982): Electrophysiological properties of neocortical neurons in vitro. *J. Neurophysiol.* 48:1302–1320.
7. Cordingley, G.E., and Somjen, G.G. (1978): The clearing of excess potassium from extracellular space in spinal cord and cerebral cortex. *Brain Res.* 151:291–306.
8. Eayrs, J.T., and Goodhead, B. (1959): Postnatal development of the cerebral cortex in the rat. *J. Anat.* 93:385–402.

9. Gardette, R., Delano, M., Dupont, J.L., and Crepel, F. (1985): Electrophysiological studies on the postnatal development of intracerebellar nuclei neurons in rat cerebellar slices maintained in vitro. II. Membrane conductances. *Dev. Brain Res.* 20:97–106.
10. Gutnick, M.J., Connors, B.W., and Prince, D.A. (1982): Mechanisms of neocortical epileptogenesis in vitro. *J. Neurophysiol.* 48:1321–1335.
11. Gutnick, M.J., and Prince, D.A. (1972): Thalamocortical relay neurons: antidromic invasion of spikes from a cortical epileptogenic focus. *Science* 176:424–426.
12. Hablitz, J.J. (1984): Picrotoxin-induced epileptiform activity in hippocampus: role of endogenous versus synaptic factors. *J. Neurophysiol.* 51:1011–1027.
13. Hablitz, J.J., Heinemann, U., and Weiss, D.S. (1986): Cellular and ionic changes during epileptiform activity in the immature neocortex. *Soc. Neurosci. Abstr.* 12:727.
14. Jahnsen, H. (1986): Electrophysiological characteristics of neurones in the guinea-pig deep cerebellar nuclei *in vitro*. *J. Physiol.* (Lond) 372:129–147.
15. Johnson, R., and Armstrong-James, M. (1970): Morphology of superficial postnatal cerebral cortex with special reference to synapses. *Z. Zellforsch.* 110:540–558.
16. Johnston, D., and Brown, T.H. (1981): Giant synaptic potential hypothesis for epileptiform activity. *Science* 211:294–297.
17. Kraig, R.P., and Nicholson, C. (1978): Extracellular ionic variations during spreading depression. *Neuroscience* 3:1045–1059.
18. Llinas, R., and Yarom, Y. (1981): Properties and distributions of ionic conductances generating electroresponsiveness of mammalian inferior olivary neurones *in vitro*. *J. Physiol.* (Lond) 315:569–584.
19. Lothman, E., LaManna, J., Cordingley, G., Rosenthal, M., and Somjen, G. (1975): Responses of electrical potential, potassium levels, and oxidative metabolic activity of the cerebral neocortex of cats. *Brain Res.* 88:15–36.
20. Lux, H.D., Heinemann, U., and Dietzel, I. (1986): Ionic changes and alterations in the size of the extracellular space during epileptic activity. In: *Advances in Neurology*, Vol. 44, edited by A.V. Delgado-Escueta, A.A. Ward, Jr., D.M. Woodbury, and R.J. Porter, pp. 619–639. Raven Press, New York.
21. MacVicar, B.A., and Dudek, F.E. (1981): Electrotonic coupling between pyramidal cells: a direct demonstration in rat hippocampal slices. *Science* 213:782–785.
22. Matsumoto, H., and Ajmone-Marsan, C. (1964): Cortical cellular phenomena in experimental epilepsy: ictal manifestations. *Exp. Neurol.* 9:305–326.
23. McCormick, D.A., Connors, B.W., Lighthall, J.W., and Prince, D.A. (1985): Comparative electrophysiology of pyramidal and sparsely spiny stellate neurons of the neocortex. *J. Neurophysiol.* 54:782–806.
24. Miller, M. (1981): Maturation of rat visual cortex. I. A quantitative study of Golgi-impregnated pyramidal neurons. *J. Neurocytol.* 10:859–878.
25. Miller, M., and Peters, A. (1981): Maturation of rat visual cortex. II. Combined Golgi-electron microscope study of pyramidal neurons. *J. Comp. Neurol.* 203:555–573.
26. Prince, D.A., and Gutnick, M.J. (1972): Neuronal activities in epileptogenic foci of immature cortex. *Brain Res.* 45:455–468.
27. Prince, D.A., and Schwartzkroin, P.A. (1978): Nonsynaptic mechanisms in epileptogenesis. In: *Abnormal Neuronal Discharges*, edited by N. Chalazonitis and M. Boisson, pp. 1–12. Raven Press, New York.
28. Schwartzkroin, P.A. (1982): Development of rabbit hippocampus: physiology. *Dev. Brain Res.* 2:469–486.
29. Schwartzkroin, P.A., and Künkel, D.D. (1982): Electrophysiology and morphology of the developing hippocampus of fetal rabbits. *J. Neurosci.* 2:448–462.
30. Sloan, N., and Jasper, H. (1950): The identity of spreading depression and "suppression." *Electroencephalogr. Clin. Neurophysiol.* 2:59–78.

31. Spain, W.J., Schwindt, P.C., and Crill, W.E. (1987): Anomalous rectification in neurons from cat sensorimotor cortex in vitro. *J. Neurophysiol.* 57:1555–1576.
32. Stafstrom, C.E., Schwindt, P.C., and Crill, W.E. (1984): Repetitive firing in layer V neurons from cat neocortex in vitro. *J. Neurophysiol.* 52:264–277.
33. Stafstrom, C.E., Schwindt, P.C., Chubb, M.C., and Crill, W.E. (1985): Properties of persistent sodium conductance and calcium conductance of layer V neurons from cat sensimotor cortex in vitro. *J. Neurophysiol.* 53:153–170.
34. Sutor, B., and Zieglgänsberger, W. (1987): A low-voltage activated, transient calcium current is responsible for the time-dependent depolarizing inward rectification of rat neocortical neurons in vitro. *Pflugers Arch.* 410:102–111.
35. Swann, J.W., and Brady, R.J. (1984): Penicillin-induced epileptogenesis in immature rat CA3 hippocampal pyramidal cells. *Dev. Brain Res.* 12:243–254.
36. Swann, J.W., Smith, K.L., and Brady, R.J. (1986): Extracellular K^+ accumulation during penicillin-induced epileptogenesis in the CA3 region of immature rat hippocampus. *Dev. Brain Res.* 30:243–255.
37. Udea, M., and Bureš, J. (1977): Differential effects of cortical spreading depression on epileptic foci induced by various convulsants. *Electroencephalogr. Clin. Neurophysiol.* 43:666–674.
38. Van Harreveld, A., and Stamm, J.S. (1953): Spreading cortical convulsions and depressions. *J. Neurophysiol.* 16:352–366.
39. Van Harreveld, A., and Stamm, J.S. (1955): Cortical responses to Metrazol and sensory stimulation in the rabbit. *Electroencephalogr. Clin. Neurophysiol.* 7:363–370.
40. Vrensen, G., De Groot, D., and Nunes-Cardozo, J. (1977): Postnatal development of neurons and synapses in the visual and motor cortex of rabbits: a quantitative light and electron microscopic study. *Brain Res. Bull.* 2:405–416.
41. Weiss, D.S., and Hablitz, J.J. (1984): Interaction of penicillin and pentobarbital with inhibitory synaptic mechanisms in neocortex. *Cell. Mol. Neurobiol.* 4:301–317.
42. Wong, R.K.S., and Prince, D.A. (1979): Dendritic mechanisms underlying penicillin-induced epileptiform activity. *Science* 204:1228–1231.

INDEX

Acetylcholine, 93, 155, 156, 170, 173, 179; nicotinic, 187
ACTH, 13, 14; for infantile spasms, 134–38, 143; *vs.* prednisone in infantile-spasm treatment, 144; and rats, 135
Adenosine, 190
Adenosine monophosphate, 174
Adrenocorticotropic hormone. *See* ACTH
ADs (afterdischarges), 248, 249, 253, 255
AEPs (auditory evoked potentials), 265–67, 275, 278–79, 281–83
Afferents: acetylcholine, 87; geniculocortical, 114, 115, 118, 121; substantia nigra, 256
Afterdischarges (ADs), 248, 249, 253, 255
Afterhyperpolarization (AHP), 163, 213, 218, 219, 234
AHP (afterhyperpolarization), 163, 213, 218, 219, 234
Akinesia, 132
α-bungarotoxin, 170
Alpha-methylparatyrosine, 141
Alpha rhythm, 19–20
Amblyopia, 50, 51, 155; in children, 9; deprivation, 50; in monkeys, 8; occlusion, 69; patching therapy for, 57, 69; strabismic, 5, 272
Amblyopia ex anopsia, 75–88
Amines, 106. *See also* Octopamine
Amino acids, 172
Amphibians, 111
Androgen, 11
Animals: darkness-reared, 45, 50, 117–18; and maternal deprivation, 14. *See also* Cats; Chicks; Kittens; Mice; Monkeys; Rabbits; Rats
Anisometropia, 50
Anophthalmia, 5
Antidepressants, tricyclic, 141
Aplysia, 88, 93, 105–6
Argamblyopia, unilateral, 7
Arrest seizures, in spike-and-wave epileptic mice, 30–34, 40, 41
Aspartate, 170
Asphyxia, perinatal, 281
Ataxia, in spike-and-wave epileptic mice, 30, 35
Atrophy, optic, 5; in children, 7
Attardo, Linda, 161–85
Auditory evoked potentials. *See* AEPs
Automatisms, behavioral, 248
Autoradiography, 86, 162; transneuronal, 115, 117
Autoreceptors, presynaptic, 256
Axodendritic proliferation, 6
Axolotls, foreign nerves in, 68

Baclofen, 186
Barbiturates, GABA and, 187
Barnes, Eugene M., Jr., 156, 186–97
Barrett, J. N., 163
Behavior, neurons and, 10
Benzodiazepines, 187
Berger, Hans, 29
Beta-adrenoceptors, 77, 83, 85–88, 105. *See also* Isoproterenol; Timolol
β-alanine, 191
Beta-receptors, 105, 195
Bethanechol, 87
Bicuculline, 186, 191, 207, 208, 235, 239, 256, 278
Bicyclophosphates, 187
Binocular recovery, 54
Birdsong, 11–12; learning of, 4, 5; nature of, 11; unaffected by deafness, 11
Birth defects, abnormality of fetal electrical activity as cause of, 126
Blakemore, C., 50, 51
Blockade, binocular impulse, *See* Tetrodotoxin (TTX)
Blood–brain barrier, 248, 251
Boutons, terminal, 151
Brain: acetylcholine level of, 4; alpha rhythm of, 19–20; cells of, 7; developing, 151–284; electrical activity of, 16–20, 151;

Brain (*cont.*)
epilepsy and, x, 198; epileptiform discharge in immature, 198–99; growth of human, 263–64; maturational changes in human, 263–76; norepinephrine level of, 4; ontogeny of, ix; pathophysiology of development of, 280–84; in utero, 17; structure-function relationships in, 151–284. *See also* Central nervous system
Brainstem, as source of infantile spasms, 138–39, 141

CA. *See* Catecholamines
Cachexia, 13
Calcium, 179; in hippocampal neurons, 232, 234; and long-term potentiation, 105; in neurons, 152, 163, 165, 167, 221, 232, 234; and potassium hyperpolarization, 239
cAMP, 105
Cannon, W. B., 6
Cat: acute deafferentation in, 8; and cellular plasticity, 4; geniculocortical afferents in, 114; lateral geniculate nucleus in, 6; and monocular deprivation, 81–85, 87–88; ocular dominance columns of, 113–19; REM sleep of, 143; strabismus in, 7–8; synaptic development in visual cortex of, 6; tetrodotoxin-treated, 118–19; VEP of, 278; visual system of, 6. *See also* Kitten
Catabolism, GABA, 186
Cataracts, 50; congenital, 5
Catecholamines, 76–77, 86, 93; neuron sensitivity to, 172. *See also* Dopamine; Norepinephrine (NE)
Cells: brain, 7 (*see also* Neurons); cultured, 161–80; deafferentation of stellate, 7; environmental "imprinting" of, 10; functional state of brain, 9; in visual cortex, 45
Central nervous system (CNS), 93; anatomic circuitry of, 3; development of human, 3–4, 263–64; diseases of, ix, 15, 154; hospitalism and, 13; immature, 151–284; infantile spasms as dysfunction of, 136–38; insult to, ix, 15; ontogeny of, ix; and seizures, 247, 249–58; versatility of, 75
Cerebral cortex: GABA-mediated inhibition in, 7; undercutting, 6–7
Channels, calcium, 190
Chemosensitivity, of cultured neurons, 170–74
Chick: brain of, 194; cerebrum of, 189; seizures in, 247
Children: binocular vision of, 9; chromatic vision in, 9; and epilepsy, 6 (*see also* Spike-and-wave epilepsy); maternally deprived, 14, in post–WWII England, 13. *See also* Infants
Chlorine, neurons and, 191
Cholecystokinin, 170
Choline acetyltransferase, 169, 174, 190, 194
Chow, K. L., 198, 200
Chromatography, liquid, 138
Clonazepam, 192
Clonus, in kindled rats, 249
CNS. *See* Central nervous system
Coleman, M., 137
Columns: ocular dominance, 111, 113–26; orientation, 111, 112–13
Compensation, heterologous, 86
Connors, B. W., 213
Convulsants, 247, 251. *See also* Penicillin
Convulsions: febrile, 138; tonic-clonic, 253. *See also* Infantile spasms; Seizures
Cornea, scarred, 50
Cortex, cholinergic input to, 4, 139. *See also* Cerebral cortex; Visual cortex
Corticosteroids, 134–37, 143, 144
Corticotropin, 13, 14
Cotransmitters, 179
Coupling, electrotonic, 208, 212
Courchesne, E., 276
Coyle, J. T., 194
Crayfish, activity-dependent modulation in, 106
Criticality, ontogenetic, 135
CT. *See* Tomography
Cynader, M. S., 117, 118

Daw, N. W., 85
Deafferentation, 7, 29; in cats, 8; and epileptogenesis, 6
Death: hospitalism and early, 13; due to tonic-clonic convulsions, 253
Decarboxylase. *See* Glutamate decarboxylase
Deguchi, T., 169
Dendrites, 154, 253; GABA and, 170
Deoxyglucose (DG), 253, 256
Deoxyglucose method, 115
Depolarizations, 204, 216–22, 240–42; GABA-induced, 235; membrane, 201; in

neurotransmitters, 179; rebound, 215–16, 220–21. *See also* LLD (long-lasting depolarization)
Depolarizing shifts (DSs), 206–7
Depolarizing shifts, paroxysmal. *See* PDSs
Depression, homosynaptic, 92, 93
Deprivation. *See* Visual deprivation
Desensitization, of GABA channels, 195
Developmental neurophysiology, 152; clinical neurology and, 15–20; importance of, ix
DG (deoxyglucose), 253, 256
Dinitrochlorobenzene, 136
DNA sequences, 155
Dopamine, 93, 179, 258; and infantile spasms, 137
Down's syndrome, infantile spasms and, 137
Dreyfus-Brisac, C., 17
Droogleever-Fortuyn, J., 30
Drucker-Colín, R., 143
Drugs: anticonvulsant, 255–56; convulsant, 247, 251 (*see also* Penicillin)
DSs (depolarizing shifts), 206–7; paroxysmal (*see* PDSs)
Dubin, M. W., 112
Ducky. *See* Mice, spike-and-wave epilepsy in
Dunwiddie, T. V., 40
Dwarfism, psychosocial, 14
Dye coupling, 208, 212

ECoG. *See* Electrocorticogram
ECS (electroconvulsive shock), 247, 258
Education, developmental neurophysiology and, ix
EEG. *See* Electroencephalogram
Efferents, substantia nigra, 256
Eimas, P., 12
Electroconvulsive shock (ECS), 247, 258
Electrocorticogram (ECoG), 31
Electrodynamic theory of development, 152
Electroencephalogram, 16–20, 131–33, 152; limitations of, 16
Electrogenesis, cortical, 277, 278
Electron microscopy, 6, 151, 162
Electrophysiology, 161–62; of cortical maturation, 263–84; of immature neocortical neurons, 198–209; of rabbit hippocampus, 225–44
EMPs (eye-movement potentials), 272, 283
Enkephalin, 180
Enna, S. J., 189, 194
Enucleation, visual, in children, 5–7
Environment, 10
Enzymes: neurotransmitter-synthesizing, 162, 174, 179. *See also* Choline acetyltransferase; Glutamate decarboxylase; Tyrosine hydroxylase
Epilepsy, x, 15–16, 30, 155, 229; and brain development, 156; in children, 6, 15–16, 20 (*see also* Infantile spasms); generalized, 16; genes of, 155; and immature brain insult, 198; and infantile spasms, 135; kindling model of, 248–53; in mice, 29; pathogenesis of, 209; petit mal, 31–32; rolandic, 16; sensory periphery and, ix; spike-and-wave (*see* Spike-and-wave epilepsy). *See also* Infantile spasms; Seizures; Status epilepticus
Epileptogenesis, 6, 157, 198, 249; age as factor in, 249–53; and hippocampal formation, 225; in immature brain, 222; in immature neocortex, 205–8; and kindling, 248–53
EPs (evoked potentials), 264–84; auditory (*see* AEPs); visual (*see* VEPs)
EPSPs (excitatory postsynaptic potentials), 204, 212, 217
EPSP-IPSP sequence, 204
ERPs (event-related potentials), 264, 274, 276–77, 280–84; neurogenesis of, 276–80
Ethology, neurophysiology and, 10
Event-related potentials. *See* ERPs
Evoked potentials. *See* EPs
Eye-movement potentials (EMPs), 272, 283

Facilitation, heterosynaptic, 92, 93, 105
Farrell, D., 30
Fetus: electrical activity in, 126; large head of human, 75; retinogeniculate transmission in, 110
Fibroplasia, retrolental, 5
Fisher, Robin S., 161–85
5-Hydroxyindoleacetic acid (5-HIAA), 137, 138
5-Hydroxytryptophan (5-HTP), 137
Flunitrazepam, 187, 189, 192, 235
Flurothyl, 251, 258
Forebrain, neurons of, 4
Freeman, R. D., 47
Frost, James D., Jr., 131–47

GABA (gamma-aminobutyric acid), 7, 155–57, 169–71, 173, 186–95, 204–5, 234–35, 256; hyperpolarizing effect of, 187; in substantia nigra, 255; transmission of, 191–95
$GABA_A$, 186, 189
$GABA_B$, 186
GABA-T (GABA 2-ketoglutarate transaminase), 186
GABA 2-ketoglutarate transaminase (GABA-T), 186
GAD (glutamic acid decarboxylase), 7, 169, 180, 204–5, 237, 253
Gamma-aminobutyric acid. *See* GABA
Genes, 152; potassium, 155; sodium, 155
Genetics, neurophysiology and molecular, 155
Gibbs, E. L., 29, 131, 132
Gibbs, F. A., 29, 131, 132
Glaucoma, congenital, 5
Glucocorticoids, 135; in rats, 13, 14; risk of in infantile-spasm treatment, 143–44
Glutamate, 170, 171, 186
Glutamate decarboxylase, 186, 188–89, 190–95
Glutamic acid, 186
Glutamic acid decarboxylase (GAD), 7, 169, 180, 204–5, 237, 253
Glycine, 155, 170, 171, 173
Goldfish, retinotectal projection of, 111–12
Golgi material, 115,
Golgi technique, 212, 281
Golgi type II cells. *See* Cells, stellate
Graziani, L. J., 267
Guinea pigs, myoclonus in, 137
Gutnick, M. J., 217

Hablitz, John J., 156, 212–24
Haglund, Michael M., 225–46
Harris, W. A., 111, 115, 117, 118, 121
Harrison, R. G., 156
Heart, neurons and muscle of, 179
Hebb, D. O., 9, 92
Hebb synapse, 122
Heinemann, Uwe, 219
Heschl's gyri, 267
Hilpert, P., 276
Hippocampus, x, 14, 225; developmental electrophysiology of rabbit, 225–44; rabbit, 157, 204, 225–44; slices of, 94–106, 212; synaptic plasticity in, 92–106
Hirsch, H. V. B., 113
Holmes, G. L., 256
Homeostasis, 240
Homovanillic acid (HVA), 137, 138
Hopkins, William F., 5, 92–109
Hormones, gonadal steroid, 256
Horseradish peroxidase (HRP), 114
Hospitalism, 13
Hrachovy, Richard A., 131–47
HRP (horseradish peroxidase), 114
Hubel, D. H., ix, 30, 45, 47, 50, 75, 76, 92, 112
HVA (homovanillic acid), 137, 138
HVc (hyperstriatum ventrale pars caudale), 11
Hydén, H., 9
Hyperexcitability, 242; in immature rabbit hippocampus, 237, 239
Hyperinnervation, NE, 35
Hyperpolarization, 241–42; potassium, 239
Hyperstriatum ventrale pars caudale (HVc), 11
Hypoxia, 135, 136
Hypsarrhythmia, 131, 132, 135, 136, 138, 143; variations of, 133

Indoleamines, 93, 105, 138. *See also* Serotonin
Infantile spasms, 15, 131–44; electroencephalographic patterns of, 132–33; and epilepsy, 135; immunologic hypothesis for, 135–36; nature of, 131–32; and sleep patterns, 138–41; spontaneous remission of, 136; steroids for, 255; types of, 132
Infants, human: and centrality of mother, 12–13; electrical activity in brain of, 16–20; hearing of, 12; and infantile spasms (*see* Infantile spasms); preterm, 263–84; seizures of (*see* Infantile spasms); VLBW (very low-birth-weight), 267. *See also* Children
Inhibitory postsynaptic potentials. *See* IPSPs
Innervation, locus ceruleus, 37
Interneurons, 173; GABAergic, 169, 204; inhibitory, 205, 232, 235, 237
Ionophores, 237
Ions, 151; chloride, 186, 189; magnesium, 170; sodium, 189
Iontophoresis, of GABA, 235
IPSPs (inhibitory postsynaptic potentials),

204, 232; hyperpolarizing, 229, 234, 235, 237, 239, 241
Ishida, I., 169
Isoproterenol, 95–96, 100–102
Isotope flux, 189, 190
Ito, M., 137

Jackson, Hughlings, 40, 155
Jackson, Meyer B., 156, 161–85
Japanese (lang.), consonantal peculiarities of, 12
Jasper, H. H., 29, 30
Johnston, Daniel, 5, 92–109
Johnston, M. V., 138
Jonsson, G., 83

Kainate, 171–73
Kainic acid, 251–53, 256
Kalil, R. E., 118
Kasamatsu, Takuji, 5, 75–91
Kaufman, L. M., 163
Kellaway, Peter, 3–27, 138
Kindling, 248–53; of rats, 256
Kirkwood, P. A., 110
Kittens: experimental amblyopia ex anopsia in, 75–88; and jumping stand, 57; ocular dominance columns of, 124–25; and spiking, 8; stimulus orientation in, 112; VEP in, 279; visual deprivation of, 45–72, 92, 93, 114, 115. *See also* Cats
Klawans, H. L., Jr., 137
Kostovic, I., 279
Kraut, M. A., 277
Kriegstein, Arnold R., 156, 198–211
Künkel, Dennis D., 225–46
Kurtzberg, Diane, 263–87

Lacy, J. R., 134
Lamb, evoked potentials in fetal, 277
Lambda complex, 272
Lambda response, 283
Lashley, Karl, 57
LC. *See* Locus ceruleus
Learning: by central nervous system, 92, 93; norepinephrine and, 106
Lethargic. *See* Mice, spike-and-wave epilepsy in
Leveille, Paula, 161–85
Leventhal, A. G., 113
Levitt, P., 39
LGN. *See* Nucleus, lateral geniculate
Liesegang method, 114, 115
LLD (long-lasting depolarization), 218–22
Locus ceruleus, 4–5, 32, 33, 105, 172; of mice, 41; neurons of, 139, 141
Long-lasting depolarization (LLD), 218–22
Long-term potentiation (LTP), 92–106
Lorenz, K. Z., 10
LTP (long-term potentiation), 92–106
Lucifer Yellow, 208, 212
Lymphocytes, 136

Macaque, effects of monocular deprivation on, 49
Mandel, P., 135
Manganese, as calcium blocker, 234
Maps: cortical, 4; iontophoretic, 170; retinotopic, 111–12
Marasmus, 13
Martin, F., 135
Mastronarde, D. N., 121
MD (monocular deprivation). *See* Visual deprivation
Memory: nervous system and, 92, 93; norepinephrine and, 106
Meningitis, 135, 136
Metabolism, inborn errors of, 143
Metabolites, CSF, 137, 138
Methysergide, 137
MHPG. *See* 3-Methoxy-4-hydroxyphenylethylene glycol
Mice: cell cultures of, 163; darkness-reared, 7; epilepsy in, 29, 155; seizures in, 247; spike-and-wave epilepsy in, 30–41
Michaelis-Menten kinetics, 191
Microphthalmia, 5
Mitchell, Donald E., 4, 45–74
Mocha^{2J}. *See* Mice, spike-and-wave epilepsy in
Modulation, noradrenergic, 92–106
Mollusks. See *Aplysia*
Monkeys: amblyopia in, 8; cortex of, 278; fetal, 277; geniculocortical afferents in, 114; neocortex of, 7; and neurons, 112; ocular dominance columns of, 115–17; seizures in, 247; synapses in, 280; visual deprivation in, 49, 54–55, 65, 115
Monoamine hypothesis, 93
Monocular deprivation. *See* Visual deprivation
Montelli, T. C. B., 136
Morimatsu, Y., 138

Moshé, Solomon L., 157, 247–62
Mota, N. G. S., 136
Motoneurons, 169; cholinergic, 174
Mouse. *See* Mice
Movshon, J. A., 68
Mower, G. D., 118
Mueller, Alan L., 40, 225–46
Muscimol, 186, 187, 189, 191, 192, 235, 256, 258
Muscle: cultured, 162; neurons and heart, 179
Myelination, 135, 270
Myoclonus, 137; focal, 30
Myopia, in monkeys, 55

Nausieda, P. A., 137
Nauta, W. J. H., 30
Nauta method, 114, 116
NE. *See* Norepinephrine
Nelson, P. G., 162
Neocortex, 86; epileptogenesis in immature, 205–8; postnatal development of, 212–22
Neonatology, developmental neurophysiology and, x
Nerves, foreign, 68
Nervous system: activity-dependent modulation and, 106; learning by, 92, 93, neurons and, 110–26; and norepinephrine, 93. *See also* Central nervous system
Neurites, 151, 180
Neurobiology, ix; developmental, 161; of learning/development, 106
Neurobiotaxis, 152
Neuroblastoma-glioma, 170
Neuroblasts, 3
Neuroembryology, 151
Neurofibrils, 190
Neurogenesis, 151; intracortical, 281
Neurogenetics, of spike-and-wave epilepsy, 29–41
Neurohormones, 86
Neurological and Electroencephalographic Studies in Infancy (Kellaway/Petersén), x
Neurology: developmental neurophysiology and clinical, 15–20; pediatric, ix
Neuromodulation, activity-dependent, 92, 93, 105, 106
Neurons, 151; action potentials in cultured, 163–70; of birds, 11; calcium and, 152, 163, 165, 167, 221; catecholamine, 176; chemosensitivity of cultured, 170–74; CNS, 30; convulsant-treated neocortical, 212–22; cortical, 141, 263; during cortical synaptogenesis, 4; cultured, 161–80; electrical activity of, 110–26; and epilepsy, x; excitability in, 152–57; GABAergic, 156–57; GABA-releasing, 186; hippocampal, 165, 167; immature, 213–16; immature neocortical, 198–209; ion channels of, 156; in kitten brain, 6–7; neocortical, 198–222; neuroblasts and, 3; noradrenergic, 139; potassium and, 152, 163, 165, 167; serotonergic, 139; during sleep, 139–41; sodium and, 152, 163, 165, 167–69, 190, 221; stellate, 7; thalamic, 141; transmitter receptors of, 156. *See also* Interneurons; Motoneurons
Neuropeptides, 86
Neurophysiology, 151, 162; developmental (*see* Developmental neurophysiology); ethology and, 10; molecular genetics and, 155
Neuropil, intracortical, 270
Neurotoxins, 170
Neurotransmission, 154; ontogeny of, 187–89
Neurotransmitters, 86, 162; components of, 162; CSF, 137, 138; and depolarization, 179; development of, 174–80; effects of maturation on, 253; responses to, 173; sensitivity of, 170. *See also* GABA; Receptors, neurotransmitter
Nirenberg, M., 155
NMDA (*N*-methyl-D-aspartic acid), 171–73
Noebels, Jeffrey L., 29–44, 151–60
NonREM. *See* Sleep, nonREM (NREM)
Norepinephrine (NE), 4, 5, 32, 76–77, 83–88, 141, 155, 172, 174, 179, 253; and infantile spasms, 137; and LTP, 94–106; and memory/learning, 93, 106; and spike-and-wave epileptic mice, 39–40
NREM. *See* Sleep, nonREM (NREM)
Nucleotides, 179
Nucleus, lateral geniculate (LGN), 111, 112–13, 115, 117, 121

Occluder, use of on kitten, 46, 57
Occlusion: alternating monocular, 125; monocular, 122, 125; reverse, 51–57, 61–70. *See also* Visual deprivation

Octopamine, 106
Olson, C. R., 47
Opiates, 170
Organization, reorganization and, 10
Ouabain, 241

Parachlorophenylalanine, 137
Paroxysmal depolarizing shifts. *See* PDSs
Patch electrodes, 162
Patching therapy, 57, 69–70
Pathophysiology, of cortical maturation, 280–84
PDSs (paroxysmal depolarizing shifts), 216–18, 220
Penfield, W., 30
Penicillin: as convulsant, 199, 205, 247; and spike-and-wave epilepsy, 30, 35
Penry, J. K., 134
Pentylenetetrazol, 256
pEPSP. *See* Population excitatory postsynaptic potential
Peptides, 179
"Period doubling," 35
Peroxidase-antiperoxidase technique, 180
Persson, M. E., 277
Petit mal. *See* Epilepsy, petit mal
Pettigrew, J. D., 93
Pia, 203, 217
Picrotoxin, 187, 191, 239, 255
Plasticity, 3–144; synaptic, 92–106; visuocortical, 75–88
Polymorphism, in vertebrate skeletal muscle, 173
Population excitatory postsynaptic potential (pEPSP), 94–95, 97–99, 102
Postsynaptic potentials. *See* PSPs
Potassium, 179; and epileptiform activity, 219–22; in hippocampal tissue, 234; and hyperpolarization, 239; and neurons, 152, 163, 165, 167; and SD, 241–42
Potentials. *See* EPSPs; IPSPs; PSPs; pEPSPs
Potentiation: long-term (LTP), 92–106; norepinephrine and long-term, 94–106; posttetanic (PTP), 92
Prednisone, 134, 144
Primates, cortex of, 279
Prince, David A., 30, 156, 198–211
Progesterone, 256
Proliferation, axodendritic, 6
Propranolol, 77–81, 87, 99, 101–2
Proteins, excitability-regulating, 154
PSPs (postsynaptic potentials), 203–4, 208, 229, 231, 234–35; depolarizing, 232; hyperpolarizing, 229
Psychiatry, child, developmental neurophysiology and, ix
PTP (posttetanic potentiation), 92
Pulvinar, primate, 279
Purpura, D. P., x

Quisqualate, 172–73

RA (robutus archistriatalis), 11
Rabbit: electrophysiology of hippocampus of, 225–44; epileptiform activity in, 157; and spiking, 8
Radioligands, 187
Rakic, P., 111, 279
Ramon y Cajal, S., 151
Raphe, neurons of dorsal, 139, 141
Rats: ACTH and, 135; aging process in, 13; brain of, 194–95; cell cultures of, 163; kindling of, 248–53, 256; locus ceruleus of, 5; and LTP, 94–106; neocortical neurons in, 212–22; pattern vision of, 57; seizures in, 156, 247, 253–58; Sprague-Dawley, 94; stress in, 13–14
"Reazione nera," 151
Receptors: acetylcholine, 173–74; amino acid, 172–73; benzodiazepine, 187, 189, 192–95; GABA, 187, 189, 192–95, 237, 256; multiple, 173; muscarinic, 194; neurotransmitter, 156; nicotinic acetylcholine, 187, 195; NMDA, 172–73; picrotoxin, 187, 189, 194. *See also* Beta-receptors
Rectification, of hippocampal cells, 234
Reinnervation, of cortical cells, 54
Reinskov, T., 136
REM. *See* Sleep, REM
Reorganization, organization and, 10
Repolarization, cell, 242
Reserpine, 141
Retardation, infantile spasms and, 131, 133–34, 143–44
Risley prisms, 88
Ritter, W., 276
Robutus archistriatalis (RA), 11
Ross, D. L., 138

Saccades, 272

Salamanders, foreign nerves in, 68
Satoh, J., 138
Saxitoxin, 202
Schmidt, J. T., 111
Schneider, J., 135
Schwartzkroin, Philip A., 157, 225–46
Scopolamine, 87
Scott, J. P., 10
SD (spreading depression), 221–22, 239–42
Seizures, 156–57, 198, 212–13; electrically induced, 248 (*see also* kindling); ontogeny of, 247–58; in rabbits, 237–42; in rats, 156. *See also* Arrest seizures; Convulsions, febrile; Epilepsy; Infantile spasms; Wet dog shakes
Sensitive periods, 3–144; in visual development of kitten, 45–72
Sensory input, aberrations in, ix
Serotonin, 93, 105, 137, 141
Shatz, C. J., 110
Short axon cells. *See* Cells, stellate
Signals, acoustic, 12
Silverstein, F., 138
6-OHDA (6-hydroxydopamine), 76, 77, 79, 83, 85–87, 93
Sleep: neuronal aspects of, 139–41; non-REM (NREM), 139; REM, 17, 133, 138–39, 141; slow-wave, 139
SN (substantia nigra), 253–58
Sodium, and neurons, 152, 163, 165, 167–69, 190, 221
Somatostatin, 179
Sotalol, 79
Spasms, infantile. *See* Infantile spasms
Specificity, areal, 111
Spike-and-wave epilepsy, 15–16, 29–41; in mice, 30–41
Spikes, EEG, 5–9, 31–32, 132–33
"Spillover," geniculate, 117–19, 121
Spines, dendritic, 151
Spitz, R. A., 13, 14
Spreading depression (SD), 221–22, 239–42
Status epilepticus, 138; in rats, 249
Steinschneider, M., 277
Stereopsis, 6
Steroids: for infantile spasms, 255. *See also* Corticosteroids
Strabismus: amblyopia and, 50; in cats, 7–8; in children, 7; experimental, 122–25; in kittens, 114. *See also* Amblyopia, strabismic
Striatum, 172, 179
Stryker, Michael P., 9, 110–30
Substance P, 170, 179, 180
Substantia nigra (SN), 253–58
Succinic semialdehyde, 186
Sutor, Bernd, 156, 212–24
Swindale, N. V., 117, 118
Synapses, 162, 170, 186, 229; asymmetric, 232; axosomatic, 253; dendritic, 253; excitatory, 171, 232; GABAergic, 194; inhibitory, 171; intracortical, 263; morphological development of, 277
Synaptic plasticity, noradrenergic modulation of, 92–106
Synaptogenesis, 204; in chick brain, 189; cortical, 4
Synaptosomes, 189

TBPS (t-butylbicyclophosphorothionate), 187, 189
Tectum, of goldfish, 112
Tetrodotoxin (TTX), 111, 112, 118–19, 122–24, 163, 169, 170, 232
Therapy: 5-HTP, 137; hormonal, 134, 143–44; patching, 57, 69–70
3-Methoxy-4-hydroxyphenylethylene glycol (MHPG), 137, 138
Timolol, 102
Tomography (CT), 133
Tottering. *See* Mice, Spike-and-wave epilepsy in
Toxin: scorpion, 169; tetanus, 169, 189. *See also* Neurotoxins
Traub, R. D., 35
Tryptophan hydroxylase, 137
TTX. *See* Tetrodotoxin
2,4-Diaminobutyrate, 190
Tyrosine hydroxylase, 190, 195

Van Sluyters, R. C., 50, 51
Vaughan, Herbert G., Jr., 263–87
VEPs (visual evoked potentials), 265, 268–72, 277–83; flash, 270–72, 277, 283; occipital, 265, 270, 271, 283; pattern, 271–72, 283; pattern-reversal, 270–71
Verapamil, 169
Veratridine, 170
Vision: binocular, 9; deprivation of (*see* Visual deprivation); sensory periphery and, ix. *See also* Visual system
Visual cortex: electrical activity in, 9, 110–

27; of human infant, 8; layer IV of, 7, 111–17, 119; mammalian, 110–27; and monocular deprivation, 45–72, 75–88, 92
Visual deprivation, 4, 45–72, 75–88, 92, 93, 115; of cats, 81–85, 87–88; of kittens, 45–72; and human infants, 55; of monkeys, 49, 54–55, 65
Visual evoked potentials. *See* VEPs
Visual system, ix–x; aberrations in input to, 5–9; effect of sensitive period on kitten's, 45–72; sensitive period of, 3–10. *See also* Vision
Von Gudden, Bernard, ix

Weitzman, E. D., 267
West, W. J., 143
West's syndrome, 131. *See also* Infantile spasms
Wet dog shakes, 249
WGA (wheat-germ agglutinin), 114
Wheat-germ agglutinin (WGA), 114
White matter, subcortical, 114, 203, 217
Wiesel, T. N., ix, 45, 47, 50, 75, 92, 112
Wong, R. K. S., 35

Xenopus, 163, 165, 173–74
Xylocaine, 169

Zebra finch, reproductive song of, 11