Special Features of the Hippocampal Formation with Respect to Seizure Conditions*

H. L. Haas

Introduction

The hippocampus has long been known as a region particularly prone to epileptiform discharges (Kandel et al. 1961). Connections and physiology of this archaic cortical structure are relatively well characterized and a wealth of information on features favoring exaggerated neuronal activity has emerged in recent years. The lamellar organization of the hippocampus (Andersen et al. 1971) may be one of these features; it certainly has facilitated their investigation. Tissue slices cut along the lamellae, perpendicular to the axis of the structure, contain a relatively undisturbed chain of neurons which can be rigorously investigated in vitro. The results from such experiments have allowed modelling and imitation of hippocampal seizures on a computer (Traub et al. 1985). The properties of hippocampal neurons and their connections are discussed here successively for didactic reasons although they overlap functionally.

Institute of Physiology, University of Mainz, Saarstr. 21, 6500 Mainz, Federal Republic of Germany

* This study was supported by the Swiss National Science Foundation (3.002.0.84) and Stiftung für Wissenschaftliche Forschung an der Universität Zürich.

Thus, the hallmark of epileptic activity, the paroxysmal depolarization shift (PDS), could equally well be considered a synaptic (Johnston and Brown 1981) or an intrinsic event (Schwartzkroin and Prince 1980).

Synaptic Connnections

The hippocampus consists of principal neurons, densely packed in one layer of a three-layered structure, which form the members in an excitatory chain (Fig. 1). These granule cells in the dentate area and pyramidal cells in Ammon's horn are surrounded by inhibitory interneurons (basket cells) with short axons. The latter receive excitatory inputs from and are inhibitory to the former. The function of other interneurons is not yet well understood.

Synaptic Excitation

Excitatory transmitters are amino acids, glutamate and aspartate being the most prominent candidates. An exaggerated excitatory transmission, either increased release or increased postsynaptic sensitivity, is one attractive hypothesis for epileptogenesis. It

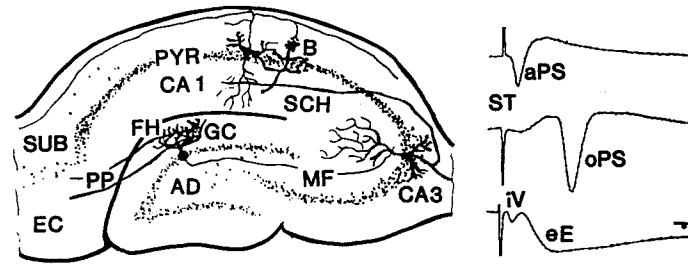

Fig. 1. Schematic representation of the hippocampal architecture and extracellularly recorded field potentials. *AD*, area dentata; *CA*, cornu ammonis; *SUB*, subiculum; *EC*, entorhinal cortex; *FH*, fissura hippocampi; *PP*, perforant path; *MF*, mossy fibers; *SCH*, Schaffer collaterals; *PYR*, pyramidal cell layer; *GC*, granule cell; *B*, basket cell; *ST*, stimulus artifacts; *aPS*, population spike in the CA1 cell body layer after alveus (antidromic) stimulation; *oPS*, synaptically evoked population spike in the same location after stimulation of the Schaffer collateral/commissural fibers; *iV*, input volley; *eE*, extracellular EPSP, synaptic field potential recorded in the apical dendritic region of CA1 after afferent stimulation. Negative is downward in this and all other figures. Calibration: 2 ms, 5 mV

Presurgical Evaluation of Epileptics
Edited by H. G. Wieser and C. E. Elger

has been suggested that the transmitters could act as excitotoxins mediating the anoxic brain damage (Meldrum 1985). CA3 pyramidal cells fire normally in bursts, and epileptiform activity in the intact structure arises from CA3 (Wong and Traub 1983). These pyramids have excitatory connections which can account for the triggering of a synchronous discharge of many cells from a single one (Miles and Wong 1983).

Electrical Synapses

Electrotonic (gap) junctions have been demonstrated between CA3 pyramids but their role in regulating neuronal excitability or synchronization is probably not important (McVicar and Dudek 1981).

Synaptic Inhibition

Classical experimental models of epilepsy like the penicillin paradigm depend on a loss of a GABAergic inhibition mediated by interneurons and a chloride conductance change (Dichter and Spencer 1969; Schwartzkroin and Prince 1977; Dingledine and Gjerstad 1980; Alger and Nicoll 1982a; Swann and Brady 1984; and author's Fig. 2). Recurrent and feed-forward inhibition is found on soma and dendrites. GABA hyperpolarizes the somata but has a mainly depolarizing effect on dendrites. The dendritic effect is nevertheless inhibitory as a large conductance change shunts the incoming excitation (Andersen et al. 1980; Alger and Nicoll 1982b). Working on (B-receptors, GABA can also activate a potassium conductance (Newberry and Nicoll 1984; Gähwiler and Brown 1985; Haas et al. 1985) which may account for pre- and postsynaptic inhibition. The inhibitory interneurons prevent CA1 pyramidal cells and dentate granule cells from expressing their intrinsic bursting properties (Wong and Prince 1979; Hablitz 1984). Transmitters or modulators that depress interneuron activity selectively are therefore epileptogenic in the hippocampus. Thus morphine has anticonvulsant properties on the whole organism but causes marked epileptiform activity in this structure.

Synaptic Plasticity

Short, subconvulsive, tetanic activation of afferent fibers leads to a persistent enhancement of excitatory transmission in the hippocampus. This long-term potentiation (LTP) was first described by Bliss et al. (1973) and has since attracted much attention as a possible learning paradigm. Repeated administration of similar tetani leads to a progressively epileptiform response with afterdischarges and finally generalized seizures. The cellular mechanisms for this kindling (Goddard et al. 1969) and LTP are probably the same although the hippocampus is not the most sensitive structure for kindling. Kindling and certain forms of epilepsy (e.g., the mirror focus) may thus be considered as a perversion of basic learning mechanisms (Fig. 3). Increased transmitter release and an enhanced postsynaptic response are likely to be involved in these phenomena. Interneuron-mediated disinhibition is not responsible, but an intrinsic disinhibition involving a reduced calcium-activated potassium conductance may operate pre- and postsynaptically (Haas and Rose 1984).

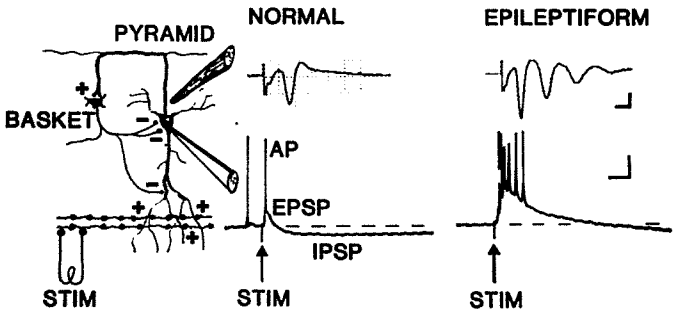

Fig. 2. Epileptiform responses to orthodromic stimulation after blockade of GABAergic basket cell inhibition in vitro. *Left*, schematic drawing of experimental situation. *Upper traces*, extracellularly recorded population spikes before and after addition of penicillin (2000 iU). *Lower traces*, intracellularly recorded EPSP - IPSP sequence before and after addition of bicuculline (10 µmol/liter) to the bathing solution. The IPSP is blocked and a large EPSP is unmasked which fires six (instead of one) action potentials. A late hyperpolarizing component of the synaptic potential is preserved. This is presumably mediated by $GABA_B$ receptors and due to a potassium conductance. (Calibrations: *upper traces*, 1 mV, 4 ms; *lower traces*, 20 mV, 50 ms)

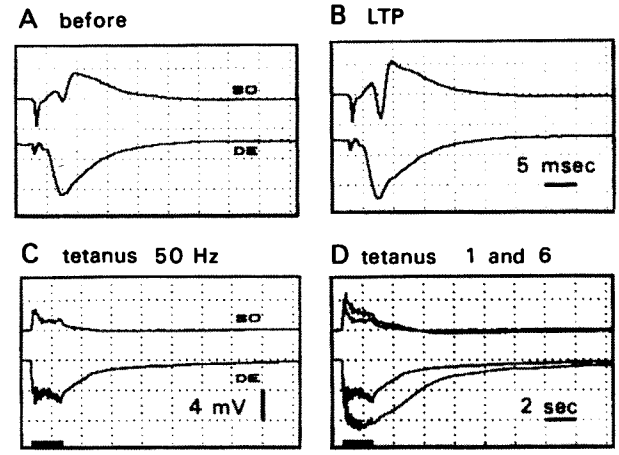

Fig. 3A–D. Long-term potentiation and "kindling" in somatic and dendritic areas of CA1. **A, B** Field potentials recorded after (orthodromic) stimulation of the Schaffer collateral/commissural input. **B** 10 min after a tetanic stimulation (2 s, 50 Hz). The extracellularly recorded EPSP and population spike are enhanced. **C** Recording of the tetanus used to elicit LTP in the same experiment (indicated by *black bar below traces).* Further tetani were given every 10 min and the response to the sixth tetanus (after 1 h) is superimposed on the first one in **C** (DC recording). This field reflects depolarization of the cells and duration of calcium inflow, which is much larger in the "kindled" situation (**D**) especially in the dendritic region. **C** and **D** show only an envelope potential, not the single population spikes (in vitro, rat)

Field Interactions

After prolonged exposure to low-Ca high-Mg media, in the absence of synaptic transmission, the pyramidal cells in the CA1 area synchronize their firing spontaneously (Jefferys and Haas 1982; Haas and Jefferys 1984; Taylor and Dudek 1984). These field bursts or spreading excitation have been shown to depend on electrical field effects (ephaptic transmission). Structures with a laminar organization, such as the hippocampus, generate large field potentials during synchronous activity. Figure 4 illustrates that population spikes are associated with a depolarization of the transmembrane potential sufficient to trigger action potentials. Although field interactions may only play a minor role in normal function, they contribute significantly to synchronization in an excited population of densely packed neurons such as the CA1 pyramids.

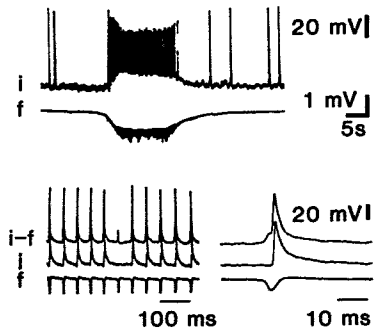

Fig. 4. Spreading excitation or field burst in the CA1 area. *i*, intracellular record; *f*, field recorded with a separate, nearby electrode; *i–f*, transmembrane potential. Lower traces show action potentials beginning with a negative (downward) potential. This reflects the electric field from the synchronous discharge of neighboring neurons, which is sufficient to entrain the recorded cell (in vitro, rat)

Extracellular Ion Concentrations

Epileptiform discharges are accompanied by a fall in Ca and an increase in K ions in the extracellular space (Heinemann et al. 1977). Both effects reinforce or cause excitation. The K accumulation is counteracted by the bufferring function of glia but if this is overrun, a wave of high K (ca. 30 mmol/liter) can move through the tissue, ignoring anatomical borders. This event is called spreading depression (Leao 1944; and author's Fig. 5). Such excitatory waves, followed by a marked and much longer lasting depression, may occur during seizures and have been seen in the retina during migraine attacks. As the transmembrane potential of the neurons approaches zero, action potentials are inactivated, and the input resistance is near zero for about 30 s. Later on, for many minutes the cell is hyperpolarized probably through an action of electrogenic pumps and perhaps an accumulation of adenosine (Greene and Haas 1985).

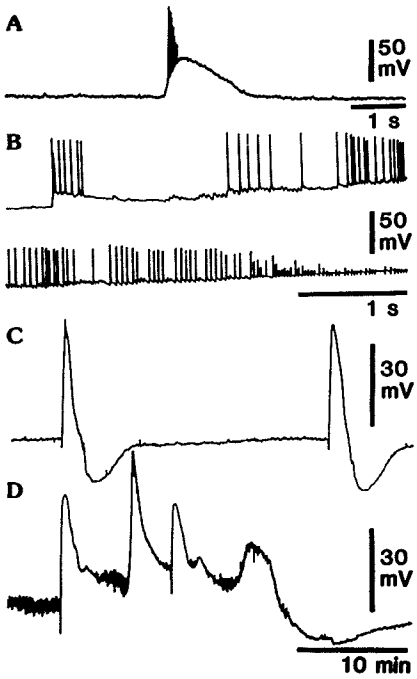

Fig. 5A–D. Intracellular recording of abnormal excitation in hippocampal slices. **A** Paroxysmal depolarization shift; **B** continuous record of a spontaneous sudden irreversible depolarization in a CA1 pyramid recorded with a cesium chloride-filled electrode (Cs has partially blocked potassium conductances and prevents repolarization). As the potential shift continues, neighboring cells become entrained; at the end of the record there is no more action potential generation but field potentials are apparent. Recording was from a completely submerged slice in which spontaneous spreading depression (SD) did not occur. **C** Two phases of spreading depression registered with a pen writer in a half-submerged slice (fast potentials are not visible); **D** same cell after (transient) treatment with ouabain (1 μmol/liter). The hyperpolarizing phase of SD has disappeared; it only recovers at the end of the record, 20 min after ouabain washout. Note the (downward) field component at the beginning of some SD phases

Intrinsic Properties of Hippocampal Neurons

Every single neuron has a certain repertoire of mechanisms which governs its response to changes in voltage or neurotransmitters. These include electrogenic pumps and ion channels which have, through their specific activation-inactivation properties and their location on the neuron (soma, dendrites), quite selective and marked influences on the firing pattern.

Voltage-Dependent Inward Currents

The TTX-sensitive Na current responsible for the rising phase of the action potential has a transient and a noninactivating component (Hotson et al. 1979). Slower transient and persistent inward currents are blocked by Cd and are most probably Ca currents (Schwartzkroin and Slawsky 1977; Johnston et al. 1980; Halliwell 1983; Brown and Griffith 1983). These can generate Ca spikes and sustained depolarizations but are normally curtailed by the action of outward potassium currents (see below). Abnormalities in the time course and extent of inactivation of inward currents may be relevant for the production of epileptic potentials such as the PDS.

Voltage-Dependent Outward Currents

Several different potassium currents have been identified in pyramidal cells. The differences between them are in the voltage ranges and the time courses of activation and inactivation. The delayed rectifier, I_K (Segal and Barker 1984) is involved in the repolarization of action potentials and an early afterhyperpolarization. I_C (Brown and Griffith 1983), a Ca-dependent current, is also rapidly activated. Tetraethylammonium (TEA) blocks these currents. Another transient current, I_A (Gustafsson et al. 1982), is blocked by 4-aminopyridine (4-AP). Both TEA and 4-AP are convulsants and increase excitatory postsynaptic potentials (EPSPs). I_M (Halliwell and Adams 1982) is probably involved in the accommodation of firing and is blocked by muscarinic agonists. A slowly activating and inactivating Ca-dependent current which is responsible for accommodation of firing (Madison and Nicoll 1984), and the long-lasting afterhyperpolarization (AHP, author's Fig. 6; Alger and Nicoll 1980; Hotson and Prince

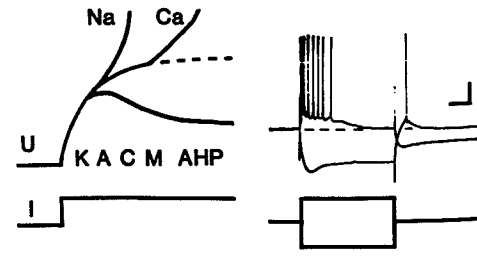

Fig. 6. Intrinsic properties of a CA1 cell. *On the left*, the deviation from the passive voltage response *(U)* of the membrane to depolarizing current injection *(I)* is shown schematically. Passive response: *exponential, broken line.* Sodium and calcium inward currents further depolarize the cell, while several potassium outward currents (I_K, I_A, I_C, I_M, I_{AHP}, see text) repolarize or prevent the neuron from reaching the firing threshold. *On the right*, response of a CA1 pyramid to ± 1-nA current injection. The depolarizing pulse evokes firing and a marked accommodation and afterhyperpolarization. The hyperpolarizing pulse evokes also a nonpassive response (I_Q)

1980) following single, or more pronounced, bursts of action potentials and Ca spikes, has been termed I_{AHP} (Adams and Lancaster 1985). This AHP is blocked by histamine (Haas and Konnerth 1983), noradrenaline (Madison and Nicoll 1982), corticotropin-releasing factor (Aldenhoff et al. 1983), cyclic AMP, and some phorbolesters (Baraban et al. 1985), and is enhanced by adenosine (Haas and Greene 1984). It seems that these substances act on the intracellular availability (sequestration) of Ca rather than directly on the K or the Ca channels. In this way the cellular excitability is linked to the genetic setup, the energy metabolism, and other biochemical events. Two of the potassium currents are sensitive to endogenous neuroactive substances (I_M and I_{AHP}) and it is likely that release of those from nerve endings normally regulates the response to excitatory signals. The frequent occurrence of seizures just after awakening may be explained by the known increased firing of locus coeruleus neurons which provide a diffuse noradrenergic innervation of the forebrain.

Conclusion

Dysregulations of all the above-mentioned mechanisms could lead to epileptogenesis. Excitatory and inhibitory events, synaptic or intrinsic, are closely interrelated and we are just beginning to understand the relative importance of the several contributing factors. At least in the hippocampus, postsynaptic regulation of excitability seems to occur mainly through a primary interaction with inhibitory events. Thus Ca spikes (and Ca currents) which are generally assumed to play a major role in epileptogenesis are not specifically and directly influenced by any drug or neuromodulator so far studied, but are profoundly modulated by K currents. Only divalent cations like Cd, Mn, Mg, Ni, and Co block Ca currents directly. These are not anticonvulsants; in fact Co ions are often used to elicit experimental epilepsy (Buchert-Rau and Sonnhof 1982). The dense packing of hippocampal principal neurons and the orientation of their dendrites, as well as the recurrent inhibition through GABAergic interneurons, predisposes the structure to synchronization and rhythmic activity. The capability of the cells to produce epileptiform potentials, large depolarization shifts, is normally under control of synaptic and intrinsic inhibitory mechanisms. Although the GABAergic inhibition has predominantly been related to epileptogenesis in the past, intrinsic inhibitions, in particular the voltage- and Ca-dependent K currents, have been attracting more attention recently.

References

Adams PR, Lancaster B (1985) Components of Ca-activated K current in rat hippocampal neurones. J Physiol 361: 23 P

Aldenhoff JB, Gruol DL, Rivier J, Vale W, Siggins GR (1983) Corticotropin releasing factor decreases postburst hyperpolarizations and excites hippocampal neurons. Science 221: 875–877

Alger BE, Nicoll RA (1980) Epileptiform burst afterhyperpolarization: calcium-dependent potassium potential in hippocampal CA1 pyramidal cells. Science 210: 1122–1124

Alger BE, Nicoll RA (1982a) Feed-forward dendritic inhibition in rat hippocampal pyramidal cells studied in vitro. J Physiol 328: 105–123

Alger BE, Nicoll RA (1982b) Pharmacological evidence for two kinds of GABA receptor on rat hippocampal pyramidal cells studied in vitro. J Physiol 328: 125–141

Andersen P, Bliss TVP, Skrede KK (1971) Lamellar organization of hippocampal excitatory pathways. Exp Brain Res 13: 222–238

Andersen P, Dingledine R, Gjerstad L, Langmoen IA, Mosfeldt-Laursen A (1980) Two different responses of hippocampal pyramidal cells to application of gamma-amino butyric acid. J Physiol 305: 279–296

Baraban JM, Snyder SH, Alger BE (1985) Protein kinase C regulates ionic conductance in hippocampal pyramidal neurons: electrophysiological effects of phorbol esters. Proc Natl Acad Sci USA 82: 2538–2542

Bliss T, Lomo T, Gardner-Medwin A (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 232: 331–374

Brown DA, Griffith WH (1983) Calcium-activated outward current in voltage-clamped hippocampal neurones of the guinea-pig. J Physiol 337: 287–301

Buchert-Rau B, Sonnhof U (1982) An analysis of the epileptogenic potency of Co^{2+} – its ability to induce acute convulsive activity in the isolated frog spinal cord. Pflügers Arch 394: 1–11

Dichter M, Spencer WA (1969) Penicillin induced interictal discharges from the cat hippocampus: 1. Characteristics and topographical features. J Neurophysiol 32: 649–663

Dingledine R, Gjerstad L (1980) Reduced inhibition during epileptiform activity in the in vitro hippocampal slice. J Physiol 305: 297–313

Gähwiler BH, Brown DA (1985) GABA B receptor-activated K^+ current in voltage-clamped CA3 pyramidal cells in hippocampal cultures. Proc Natl Acad Sci USA 82: 1558–1562

Goddard CV, McIntyre DC, Leech CK (1969) A permanent change in brain function resulting from daily electrical stimulation. Exp Neurol 25: 295–330

Greene RW, Haas HL (1985) Adenosine actions on CA1 pyramidal neurons in rat hippocampal slices. J Physiol 366: 119–127

Gustafsson B, Galvan M, Grafe P, Wigström H (1982) A transient outward current in a mammalian central neurone blocked by 4-aminopyridine. Nature 299: 252–254

Haas HL, Greene RW (1984) Adenosine enhances afterhyperpolarization and accommodation in hippocampal pyramidal cells. Pflügers Arch 402: 244–247

Haas HL, Jefferys JGR (1984) Low calcium field burst discharges of CA1 pyramidal neurones in rat hippocampal slices. J Physiol 354: 185–201

Haas HL, Konnerth A (1983) Histamine and noradrenaline decrease calcium-activated potassium conductance in hippocampal pyramidal cells. Nature 302: 432–434

Haas HL, Rose G (1984) The role of inhibitory mechanisms in hippocampal long term potentiation. Neurosci Lett 47: 301-306

Haas HL, Jefferys JGR, Slater NT, Carpenter DO (1984) Modulation of low calcium induced field bursts in the hippocampus by monoamines and cholinomimetics. Pflügers Arch 400: 28-33

Haas HL, Greene RW, Olpe H-R (1985) Stereoselectivity of l-baclofen in hippocampal slices of the rat. Neurosci Lett 55: 1-4

Hablitz JJ (1984) Picrotoxin-induced epileptiform activity in hippocampus: role of endogenous versus synaptic factors. J Neurophysiol 51: 1011-1027

Halliwell JV (1983) Calcium-loading reveals two distinct Ca-currents in voltage-clamped guinea-pig hippocampal neurons in vitro. J Physiol 341: 10-11

Halliwell JV, Adams PR (1982) Voltage-clamp analysis of muscarinic excitation in hippocampal neurons. Brain Res 250: 71-92

Heinemann U, Lux HD, Gutnick MJ (1977) Extracellular free calcium and potassium during paroxysmal activity in cerebral cortex of the cat. Exp Brain Res 27: 237-243

Hotson JR, Prince DA (1980) A calcium-activated hyperpolarization follows repetitive firing in hippocampal neurons. J Neurophysiol 43: 409-419

Hotson JR, Prince DA, Schwartzkroin PA (1979) Anomalous inward rectification in hippocampal neurons. J Neurophysiol 42: 889-895

Jefferys JGR, Haas HL (1982) Synchronized bursting of CA1 hippocampal pyramidal cells in the absence of synaptic transmission. Nature 300: 448-450

Johnston D, Brown TH (1981) Giant synaptic potential hypothesis for epileptiform activity. Science 211: 294-297

Johnston D, Hablitz JJ, Wilson WA (1980) Voltage clamp discloses slow inward currents in hippocampal burst firing neurones. Nature 286: 391-393

Kandel ER, Spencer WA, Brinley FJ (1961) Electrophysiology of hippocampal neurons. J Neurophysiol 24: 225-285

Leao AAP (1944) Spreading depression of activity in the cerebral cortex. J Neurophysiol 7: 359-390

Madison DV, Nicoll RA (1982) Noradrenaline blocks accommodation of pyramidal cell discharge in the hippocampus. Nature 299: 636-638

Madison DV, Nicoll RA (1984) Control of the repetitive discharge of rat CA1 pyramidal neurones in vitro. J Physiol 354: 319-331

McVicar BA, Dudek FE (1981) Electrotonic coupling between pyramidal cells: a direct demonstration in rat hippocampal slices. Science 213: 782-784

Meldrum B (1985) Excitatory amino acids and anoxic/ischaemic brain damage. TINS 8: 47-48

Miles R, Wong RKS (1983) Single neurones can initiate synchronized population discharge in the hippocampus. Nature 306: 371-373

Newberry NR, Nicoll RA (1984) Direct hyperpolarizing action of baclofen on hippocampal pyramidal cells. Nature 308: 450-452

Schwartzkroin PA, Prince DA (1977) Penicillin-induced epileptiform activity in the hippocampal in vitro preparation. Ann Neurol 1: 463-469

Schwartzkroin PA, Prince DA (1980) Changes in excitatory and inhibitory synaptic potentials leading to epileptogenic activity. Brain Res 183: 61-76

Schwartzkroin PA, Slawsky M (1977) Probable calcium spikes in hippocampal neurons. Brain Res 135: 157-161

Segal M, Barker JL (1984) Rat hippocampal neurons in culture: potassium conductances. J Neurophysiol 51: 1409-1433

Swann JW, Brady RJ (1984) Penicillin-induced epileptogenesis in immature rat CA3 hippocampal pyramidal cells. Dev Brain Res 12: 243-254

Taylor CP, Dudek FE (1984) Excitation of hippocampal pyramidal cells by an electrical field effect. J Neurophysiol 52: 126-142

Traub RD, Dudek FE, Taylor CP, Knowles WD (1985) Simulation of hippocampal afterdischarges synchronized by electrical interactions. Neuroscience 14: 1033-1038

Wong RKS, Prince DA (1979) Dendritic mechanisms underlying penicillin-induced epileptiform activity. Science 204: 228-231

Wong RKS, Traub RD (1983) Synchronized burst discharge in disinhibited hippocampal slice. 1. Initiation in CA2-CA3 region. J Neurophysiol 49: 442-458