the temperature, the pH, and the ionic strength. The basic amino acids such as lysine, histidine, and arginine, which do not emerge under the conditions described (Table 1), could possibly be eluted in a reasonable time at higher ionic strength or on a shorter column (or both).

Additional options for obtaining desired resolutions are the use of chiral ligands differing from proline, including other amino acids, their derivatives, or other classes of compounds. Changing the nature of the cation offers further possibilities. For instance, hydroxyproline-Cu^{2+} complexes show stereoselectivity as good as or better than that of proline (*13*).

When an L-proline ligand is used, the L enantiomer of the amino acid resolved is eluted before the corresponding D isomer (Fig. 1a). This order is reversed when a D-proline–copper complex is dissolved in the eluant (Fig. 1b), and there is no resolution with a racemic proline-copper complex in the eluant (Fig. 1c). Switching chirality of the eluant offers a useful method for distinguishing nonchiral artifacts from true enantiomers in a sample and requires only a few minutes for equilibrating the column. Retention times can be accurately reproduced (Fig. 1).

The stereoselectivity is ascribed to differences in the stability constants of diastereomeric species such as the L-proline–Cu^{2+} complex with an L-amino acid and the L-proline-Cu^{2+} complex with a D-amino acid in aqueous solution. Qualitative and quantitative differences of stability constants have been reported (*14*), and it is surprising that resolutions of amino acids similar to those described here have not been reported before (*15*).

Our results indicate the feasibility of a simple automated procedure for quantitative protein amino acid analysis with simultaneous determination of enantiomeric composition. The method will be useful, for example, in checking synthetic and naturally occurring biologically active peptides for the presence of D-amino acid components, for screening physiological fluids for D-amino acids, and for ascertaining amounts of D-amino acid enantiomers in progressively older fossils (*16*), in certain living tissues such as tooth dentin and enamel, and in lens proteins of cataract patients (*17*).

The presence of naturally occurring chiral ligands coordinated to metals and their role in the geochemical transport and distribution of enantiomers and trace elements is a question of interest arising from our study.

Our experiments establish the feasibility of resolution of underivatized α-amino acids on an ion-exchange column with a chiral aqueous eluant. LePage *et al.* (*18*) achieved resolution of *dansyl* amino acids by reverse phase chromatography and an eluant containing a zinc-chiral ligand complex. These two studies and those referred to earlier (*6*) illustrate the additional refining in separation power that can be achieved by modifying the eluant composition (*19*).

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27 March 1979

Dendritic Mechanisms Underlying Penicillin-Induced Epileptiform Activity

Abstract. *The action of penicillin on synaptically evoked dendritic activity was examined with the use of hippocampal slice preparations. Orthodromic activation of CA1 pyramidal neurons produced an excitatory-inhibitory postsynaptic potential sequence recorded intracellularly in the dendrites. Treatment with penicillin resulted in the appearance of spontaneous and synaptically evoked multipeaked field potentials and associated depolarization shifts and spike burst generation in CA1 cells. Intracellular recordings revealed that penicillin produced no detectable change in passive membrane properties of the postsynaptic dendrites. However, the inhibitory postsynaptic potential was suppressed by penicillin, resulting in the release of intrinsic dendritic burst firing during synaptic activation. These findings emphasize the role of normal patterns of dendritic burst generation in the production of intense neuronal discharge during penicillin-induced epileptiform activities.*

Application of the convulsant drug penicillin to mammalian cortex leads to the development of interictal epileptiform discharges recorded in the electrocorticogram. Intracellular recordings obtained from neurons during the genesis of such events typically show high-amplitude (20 to 30 mV) prolonged (50 to 100 msec) membrane depolarization shifts (DS's) with overriding trains of action potentials. The mechanism underlying the generation of these DS's is an important issue directly relevant to our understanding of the basic mechanisms of epilepsy. Two hypotheses have been proposed (*1*). One suggests that DS's that give rise to burst firing are summated excitatory postsynaptic potentials (EPSP's) resulting from actions of penicillin which increase excitatory synaptic transmission (*2*) or decrease inhibitory synaptic events (*3*). A second hypothesis

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attributes DS generation to alterations in active regenerative membrane properties induced by penicillin (*4*).

Neither hypothesis appears to be adequate in view of recent results. Penicillin does not significantly affect either active (*5*) or passive (*6*) membrane properties or lead to development of summated EPSP's (*6*) in the pyramidal cells of the CA1 region in slice preparations. Nonetheless, it does induce spontaneous or orthodromically evoked burst firing and epileptiform field potentials (*6*) resembling those observed in vivo (*7*). Evidence suggests that the bursts recorded in the soma are initiated at remote impulse generation sites, possibly in the apical dendrites (*6*). We therefore further investigated the mechanism of penicillin-induced epileptogenesis by recording intracellularly from the apical dendrites of CA1 neurons.

Experiments were performed on transverse slices of guinea pig hippocampus prepared and maintained in vitro (*8*). Stratum pyramidale and stratum radiatum, which contain, respectively, somata and dendrites of CA1 pyramidal cells, could be easily identified in the transilluminated slice (*8*). In initial experiments, impaled elements in stratum radiatum were identified as dendrites when intracellular horseradish peroxidase injections showed that the somata of labeled elements were located in stratum pyramidale, 150 to 350 μm from the site of impalement in stratum radiatum (*9*). We now assumed that a dendrite had been impaled on the basis of the site of microelectrode penetration and the characteristic responses to direct and orthodromic stimuli which differed from those of somata (*9*). Orthodromic input onto CA1 pyramidal cell dendrites was activated by stratum radiatum stimulation (*6*, *9*). Slices were exposed to normal perfusion medium or a solution containing sodium penicillin G (2000 I.U./ml; 3.4 m*M*). Penicillin in these concentrations had no significant effects on osmolarity or *p*H. Alternatively, micropipettes containing sodium penicillin (10,000 I.U./ml) were used to apply drugs focally by pressure injection. The results obtained were independent of the method of drug application.

During stable intradendritic penetrations, resting membrane potentials of −55 to −70 mV were recorded. When the resting potentials were lower than −60 mV, spontaneous bursts of action potentials riding on slow depolarizations occurred in both normal and penicillin-containing medium. The characteristics of these bursts have been described elsewhere (*9*). Cells with higher membrane potentials did not burst spontaneously; however, short-duration depolarizing current pulses could trigger all-or-none bursts (Fig. 1, A1) (*10*). A short-duration hyperpolarizing current pulse applied during a burst would abort the subsequent spike train and reset the membrane to the resting level, provided the hyperpolarizing pulse was of sufficient intensity to block a spike (Fig. 1, A2).

Orthodromic stimulation subthreshold for postsynaptic spike initiation evoked a depolarization-hyperpolarization sequence recorded intradendritically (Fig. 1, B1 and B2). The amplitude of the depolarization was smoothly graded in proportion to the stimulus strength. The decay phase of depolarization occurred at a rate faster than that expected for a passive process (Fig. 2A), and the hyperpolarization which followed was accompanied by an increase in membrane conductance (Fig. 1C). These observations suggest that the orthodromic input evoked an excitatory-inhibitory postsynaptic potential (EPSP-IPSP) sequence in the dendrites. Similar events are also recorded in the soma during orthodromic activation (*11*). The temporal pattern of the EPSP-IPSP sequence was such that the EPSP duration was shortened by the concomitant occurrence of an IPSP (Fig. 2A).

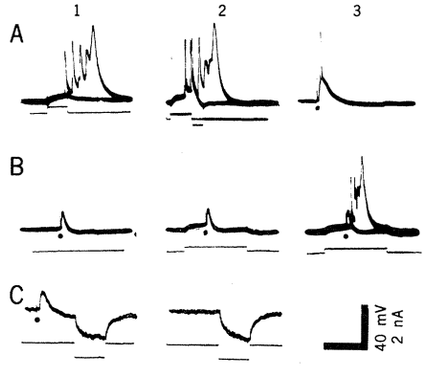

Fig. 1. Intradendritic records of orthodromically and directly evoked activities. Records of A1, A3, and B are from the same dendrite. (A1) Superimposed sweeps of responses to 20-msec depolarizing pulses, one of which evoked a burst of action potentials. (A2) Two superimposed sweeps showing one full burst response and another burst which was aborted after the second spike by a brief hyperpolarizing current pulse. The third spike was suppressed at a voltage level that is very close to that for its initiation, suggesting that the spikes are locally generated. (A3) Supramaximal orthodromic activation evokes an EPSP which triggers only a single spike. (B1 and B2) Orthodromic stimuli evoke EPSP-IPSP sequences. (B3) Superimposed sweeps showing control burst response and its blockade by an orthdromically evoked EPSP-IPSP sequence. (C) Hyperpolarizing current pulse applied during orthodromically evoked IPSP (C1) elicits a smaller voltage deflection with a briefer rise time than control (C2). Time calibration: 40 msec for (A) and (C); 80 msec for (B).

There was a marked difference in the effectiveness of orthodromic as opposed to direct stimuli in eliciting burst firing. Supramaximal orthodromic stimuli elicited only single action potentials from large-amplitude EPSP's (Fig. 1, A3) and never triggered bursts. By contrast, intradendritic depolarizing current pulses regularly evoked all-or-none bursts of action potentials even when the stimulus parameters were adjusted so that the durations and amplitudes of the current-induced membrane depolarizations did not exceed those associated with the supramaximally evoked EPSP's (compare A2 and A3 in Fig. 1). The failure of orthodromic input to evoke burst firing appeared to be related to the occurrence of the IPSP. Directly evoked bursts were blocked when depolarizing current pulses were conditioned by orthodromic stimuli timed so that the IPSP fell during the expected burst (Fig. 1, B3). We assume that the IPSP prevented burst firing by repolarizing the membrane, as in the case of hyperpolarizing current pulses (Fig. 1A), and also by producing a local conductance increase (Fig. 1C) (*12*).

When penicillin was applied to the preparation, spontaneous and orthodromically evoked multipeaked field potentials similar to those described during epileptogenesis in vivo (*7*) and in vitro (*6*) were recorded extracellularly in the stratum radiatum (Fig. 2, B5 and B6). Intradendritic recordings showed that no detectable changes in resting potential, input resistance, or voltage threshold for action-potential initiation were produced by penicillin. A significant increase in the duration, but not the amplitude, of the orthodromically evoked EPSP was observed, however [see upper (▲) and lower (■) insets and corresponding curves in Fig. 2A]. This change could be accounted for entirely by a prolongation of the decay phase of the EPSP, which could now be fitted to a single exponential with a time constant comparable to the membrane time constant [see curves (△) and (□) of Fig. 2A]. Thus EPSP's evoked in drug-treated slices appeared to decay passively, a result that would be expected if penicillin blocked a concomitantly elicited IPSP. In a total of nine intradendritic recordings, penicillin increased the half-amplitude duration of the EPSP by 67 percent (from a control average of 6 msec to 10 msec after exposure) (*13*). Figure 2, B1 and B4, illustrates the typical responses of a dendrite to direct and orthodromic stimulation be-

fore (B1 and B2) and after (B3 and B4) exposure to penicillin. Although direct stimulation could evoke bursts under both conditions (B1 and B3), orthodromic stimuli were effective only after penicillin exposure when the time course of the EPSP had been altered (see Fig. 2, B2 and B4). It may be noted that the amplitude of the EPSP evoked after the addition of penicillin (Fig. 2, B4) did not exceed that of the EPSP evoked before drug treatment (Fig. 2, B2).

Our data indicate that burst firing is an intrinsic property of hippocampal pyramidal cell dendrites. During orthodromic stimulation, this type of active response is blocked by postsynaptic inhibition. A comparable effect of distal inhibition on dendritic spikes has been reported in alligator Purkinje cells (*14*). After the application of penicillin, orthodromic stimuli become effective in evoking burst firing in the postsynaptic dendrites. This change appears to be due to the depressant action of penicillin on the γ-aminobutyric acid-mediated (*15*) IPSP in CA1 pyramidal cells, an action similar to that described in a variety of preparations (*3*). Until now, the mechanism whereby this disinhibitory action of penicillin leads to DS generation and neuronal bursting, such as that occurring during interictal epileptiform discharge, has been unclear. It has been suggested that disinhibition might enhance excitatory input to the neuron by releasing recurrent excitatory neuronal pathways (*16*). The enhanced excitation would generate summated EPSP's (DS's) which would in turn produce neuronal bursting. In the hippocampal slice preparation a different explanation for penicillin-induced DS generation is required. Our results suggest that disinhibition produced by penicillin releases a potent postsynaptic amplifying device, namely, dendritic burst firing and associated DS generation, which in turn may play a critical role in patterning the output of the neuron (*9*).

Although these results emphasize the intrinsic properties of individual neurons with respect to DS generation, it is obvious that synchronization of a group of neurons is required for the genesis of the large-amplitude multipeaked field potentials which occur during interictal epileptogenesis in the hippocampus. Our data do not bear directly on the mechanism for this synchronization; however, they do show that once disinhibition has occurred, synaptic inputs onto CA1 neurons become effective in triggering burst firing. Under these circumstances the Shaffer collateral input from CA3 neurons, which makes en passant contacts onto pyramidal cell dendrites in CA1, would be effective in synchronizing the intrinsic burst discharges in large groups of neurons (*17*). In this regard it is significant that generation of spontaneous penicillin-induced epileptiform bursts in the CA1 region of the slice depends on the integrity of CA3-CA1 connections (*6*).

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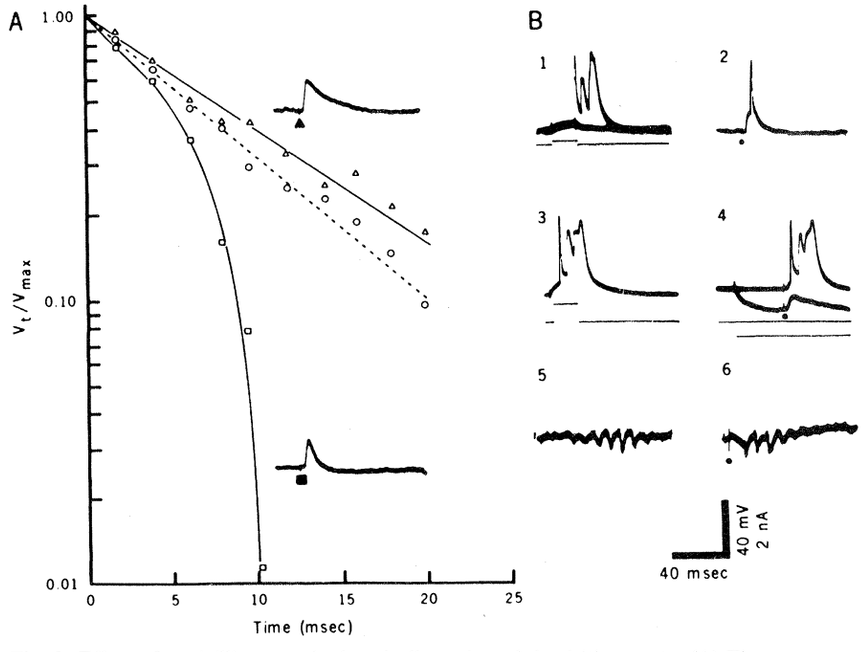

Fig. 2. Effect of penicillin on orthodromically activated dendritic events. (A) Time course of decay of EPSP's in the same neuron plotted before (□) and after (△) exposure of the slice to penicillin. The resting potential was maintained at −70 mV by intracellular current during orthodromic stimulation. Bridge circuit for current injection was checked and balanced during the onset and release of the holding current. Time course of the membrane voltage response to constant current hyperpolarizing pulse in the same cell is also plotted (○). For the synaptic events, V_{max} is peak depolarization and V_t is the magnitude of depolarization measured at a given time after the occurrence of V_{max}. For the membrane response to constant current, V_{max} is the maximum change in membrane potential and V_t the difference between the voltage change produced at a given time during the current pulse and V_{max}. Insets: Actual records of the synaptic events before [lower sweep (■) at stimulus artifact] and after [upper sweep (▲) at stimulus artifact] penicillin treatment. (B1 to B4) Responses of the same dendrite to direct (B1 and B3) and orthodromic (B2 and B4) stimulation applied before (B1 and B2) and after (B3 and B4) exposure of the slice to penicillin medium. Direct response after penicillin treatment shows only a shorter latency to burst onset related to increased current pulse amplitude (bottom traces). Hyperpolarizing pulse in superimposed sweep of B4 uncovers EPSP responsible for burst triggering. (B5 and B6) Spontaneous (B5) and orthodromically evoked (B6) multipeaked field potentials recorded after treatment with penicillin in stratum radiatum, 250 μm from stratum pyramidale. Calibrations in B6: 40 mV for B1 to B4; 80 mV for B5 and B6. Time, 40 msec.

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Behavior Maintained by Termination of a Schedule of Self-Administered Cocaine

Abstract. *Squirrel monkeys self-administered cocaine by pressing a lever while under a variable-interval schedule of reinforcement. At the same time, they terminated the availability of self-administered cocaine by pressing a second lever while under a fixed-interval schedule of reinforcement. The maintenance of behavior by scheduled drug injections and by termination of scheduled drug injections, usually considered to be processes associated with different classes of drugs, can occur simultaneously when behavior is controlled by different contingencies associated with a single drug.*

Some unexpected effects of drugs that are self-administered by laboratory animals have recently been observed (*1*). Under suitable conditions, both *d*-amphetamine and apomorphine have been found to maintain responding that leads to their injection; yet, these same drugs also suppress drinking of flavored solutions associated with their injection (*2*). Other drugs, such as pentazocine, propiram, nalorphine, and naloxone can maintain responding that either leads to or postpones their scheduled injection depending on the physiological state of the subject and the environmental conditions under which the drugs are administered (*3*). Such disparate effects suggest that factors other than the inherent properties of drugs can be critical in determining how drugs affect behavior. The identification of such factors should have important implications for the control of drug-taking behavior.

In the experiment reported here, separate responses by individual squirrel monkeys were maintained simultaneously when presses on one lever produced injections of cocaine and presses on a second lever terminated the schedule of cocaine injection. The maintenance of behavior by scheduled drug injections and by termination of scheduled drug injections, usually considered to be processes involving different classes of drugs, can occur simultaneously when behavior is controlled by different contingencies involving a single drug.

Four mature male squirrel monkeys (*Saimiri sciureus*) that had no previous experience with drugs were studied. Throughout the experiment, the monkeys had unrestricted access to food and water in their individual home cages. During daily experimental sessions, the monkeys were seated in a restraining chair equipped with a red stimulus light and two response levers (*4*); the chair was enclosed in a sound-attenuating chamber. Injections of cocaine were delivered through venous catheters (*5*) from an infusion pump located outside the chamber.

Initially, responses on a single lever produced intravenous injections of cocaine (*6*) on the average of once every 3 minutes (3-minute variable-interval schedule of cocaine injection). When responding was stable from day to day (18 to 24 sessions), a second lever was introduced to the left of the existing lever. The first response on the left lever occurring 3 minutes after the start of the session terminated the schedule of cocaine injection and started a 1-minute time-out period (3-minute fixed-interval schedule of termination). During the time-out, the stimulus light that normally illuminated the chamber was turned off, the schedules associated with each lever were stopped, and responses on the levers had no programmed consequences. At the end of the time-out, the stimulus light again illuminated the chamber and the schedules associated with each lever were restarted. This cycle was repeated 20 times per session.

Under the concurrently arranged schedules, distinctly different response rates and temporal response patterns

Table 1. Overall response rates (responses per second) on each lever for individual monkeys. Data are means based on the last three sessions of each condition; ranges are in parentheses. Protocol A: responses on the right lever initially produced injections of cocaine under a VI (variable-interval) schedule, while responses on the left lever terminated the schedule of cocaine injection under an FI (fixed-internal) schedule. The schedules associated with each lever were reversed twice. Protocol B: responses on the right lever produced injections of either cocaine or saline under a VI schedule, while responses on the left lever either terminated the schedule of injection under an FI schedule or had no programmed consequences (extinction).

Schedule		Responses per second		Sessions	Responses per second		Sessions
Left	Right	Left	Right		Left	Right	
Protocol A		*Monkey S-146*			*Monkey S-153*		
FI (termination)	VI (cocaine)	0.37 (0.33–0.41)	0.13 (0.10–0.17)	60	0.23 (0.22–0.26)	0.16 (0.14–0.17)	54
VI (cocaine)	FI (termination)	0.16 (0.14–0.18)	0.34 (0.24–0.45)	16	0.10 (0.09–0.13)	0.20 (0.18–0.23)	23
FI (termination)	VI (cocaine)	0.29 (0.24–0.37)	0.16 (0.11–0.19)	15	0.16 (0.15–0.17)	0.10 (0.08–0.11)	16
Protocol B		*Monkey S-154*			*Monkey S-332*		
FI (termination)	VI (cocaine)	0.20 (0.19–0.23)	0.14 (0.12–0.15)	62	0.18 (0.16–0.22)	0.30 (0.29–0.31)	36
FI (termination)	VI (saline)	0.06 (0.03–0.09)	0.05 (0.03–0.07)	13	0.02 (0.01–0.04)	0.04 (0.03–0.06)	5
FI (termination)*	VI (saline)	0.04 (0.02–0.06)	0.04 (0.03–0.05)	9	0.05 (0.03–0.07)	0.07 (0.03–0.10)	17
FI (termination)	VI (cocaine)	0.16 (0.15–0.17)	0.13 (0.10–0.15)	10	0.17 (0.16–0.19)	0.26 (0.25–0.27)	19
Extinction †	VI(cocaine)	0.04 (0.01–0.07)	0.18 (0.11–0.22)	18	0.02 (0.00–0.04)	0.28 (0.21–0.32)	7

*Cocaine infused before each session (*8*). †Sessions ended after 60 minutes.

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