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Microphysiology of Spinal Seizures

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CONVULSIONS OF SPINAL ORIGIN

The spinal cord has been a perenially useful testing ground of ideas concerning the functions and malfunctions of mammalian central gray matter. In the investigation of seizures, however, it has been rather neglected, perhaps because human epilepsy is customarily thought of as a disease of the brain. Yet severed from the brain, the spinal cord is capable of convulsive activity. Even in the absence of overt paroxysms, in the unstimulated spinal cord there are signs of irregular interneuron activity which is much more lively in high spinal than in decerebrate preparations (53). Intense electrical stimulation of the first cervical segment causes rhythmic contractions of the skeletal musculature during low frequency stimulation and tonic paroxysmal discharge thereafter (21). Transient hypoxia can cause persistent spontaneous discharges, as all practitioners of spinal cord electrophysiology sooner or later learn to their grief. Of the numerous stimulant drugs, strychnine has long been considered the spinal convulsant par excellence.

The minimal convulsant dose of strychnine is about the same for intact animals and decerebrate preparations as for decapitate spinal cords. Pentylenetetrazole and bemegride, on the other hand, have been considered to act primarily on the brainstem, because the minimal dose required to induce paroxysmal activity in the severed spinal cord is about 20 times higher than in preparations with intact brainstem (27,28). Yet both drugs can induce characteristic convulsive activity in spinal preparations, albeit at a high dose level (28) (Fig. 1). One may ask, therefore, whether these drugs have the same or a different mode of action in brain as in spinal cord. If the basic mechanism is identical, do the different dose levels reflect (a) a greater "affinity" for cellular elements or for subcellular organelles in the brain than in cord, (b) the same degree of affinity to the same cellular components, of which, however, there exist larger numbers in the brainstem than in the spinal gray matter, or, least probably, (c) that the drug penetrates more readily from blood into brainstem than into spinal cord?

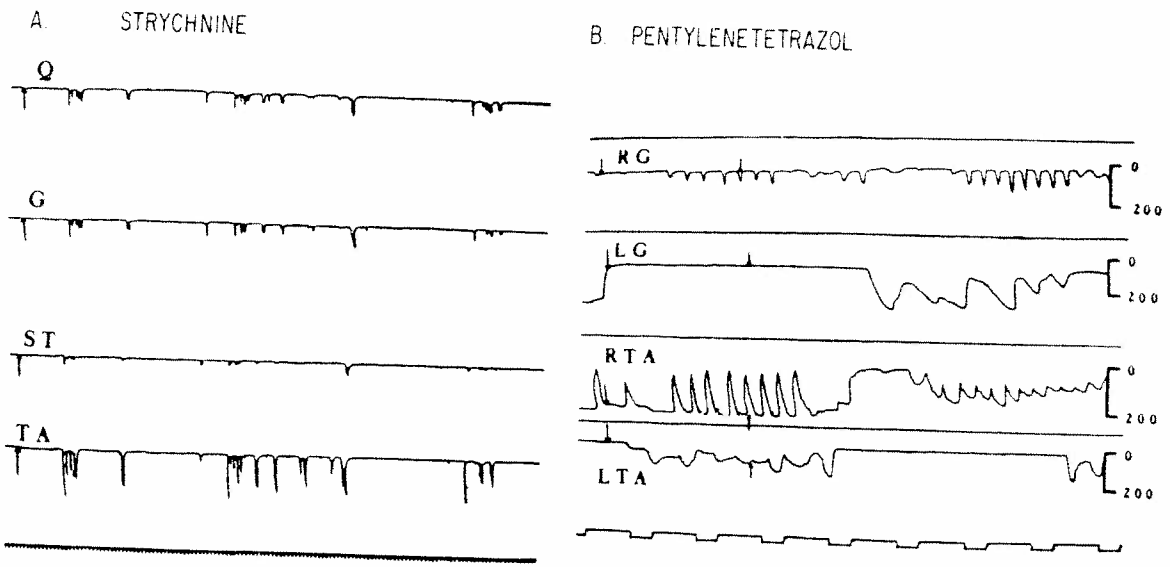

FIG. 1. Patterns of convulsion induced by strychnine **(A)** and pentylenetetrazole **(B)** in decapitate spinal cords. The contractions of individual muscles were recorded as downward deflections on a smoked paper kymograph. Q, quadriceps muscle; G, gastrocnemius; ST, semitendinosus; TA, tibialis anterior; RG, right gastrocnemius; LG, left gastrocnemius; RTA, right tibialis anterior. Time in sec. Arrows mark simultaneity in four traces. (Slightly modified from ref. 28.)

Besides relative dose level, strychnine also differs from pentylenetetrazole and bemegride in the pattern of the convulsions it induces. Cocontraction of antagonistic muscles is the rule with strychnine. The two other drugs cause convulsions that erupt now in flexors then in extensors and occasionally alternate in opposing muscle groups in rhythmic sequences (Fig. 1).

Cocontraction of antagonistic muscles under the influence of strychnine may be explained by blockade of reciprocal inhibition by the drug (7). But cocontraction is also characteristic of (a) the seizures induced by penicillin (37), a drug that leaves postsynaptic inhibition in the spinal cord unimpaired (14,17,19,39) and (b) electrically provoked seizures in intact cats (22). Yet penicillin resembles strychnine in one more respect; namely, the minimal convulsant dose is similar for intact cats (47,48,54), high spinal preparations (37), and cats rendered comatose by bilateral lesion in the midbrain reticular formation (T. Dunaway, *unpublished*). Convulsive activity of spinal origin has been reported not only in cats but also in human patients treated with massive doses of penicillin following injury causing brain damage and EEG silence (50). Large enough doses cause grand mal seizures in intact animals (48,54,58) and in decapitate spinal cords alike (37).

Since the same amount of penicillin induces seizures in intact cats as in animals with midbrain lesion and in high spinal preparations, one must wonder at which end of the neuraxis penicillin convulsions originate in an intact nervous system. Myoclonic twitching and "petit mal" type 4 to 5 per sec "runs" of waves or spike-wave complexes were characterized as centrencephalic by Prince and Farrell (47) but attributed to probably cortical origin by Gloor and Testa (24,55).

In the unanesthetized preparation with midbrain lesion, penicillin-induced tonic seizures usually appear in recordings from motor cortex before they erupt in the lumbosacral spinal cord (Fig. 2A); but in a sizeable minority of cases, the sequence is the reverse (not illustrated). During clonic convulsions, cortical waves sometimes lead, but frequently lag behind, discharges in spinal ventral root (Fig. 2B–D). The statistical incidence of cortical and spinal leading in two different experimental periods within the same preparation is illustrated in Fig. 3. During interictal discharges, motor cortex and lumbosacral spinal segments similarly alternate in leading and lagging.

Temporal sequencing need not reflect a causal relationship. Both cortical and spinal discharges may be driven by a subcortical pacemaker, e.g., in the diencephalon. This was almost certainly so whenever the cortical discharge preceded the spinal by less than 5 msec. Such short intervals, seen frequently during clonic seizures, are too brief for corticospinal conduction to take place (for cerebrospinal conduction times, see, e.g., ref. 44). Spinocortical lag times, however, usually amounted to 5 to 70 msec (modal values in different experiments between 10 and 50 msec) and are best explained by seizure activity initiated in spinal cord and conducted to cortex. For a subcortical intracranial focus to drive lumbosacral spinal segments 10 to

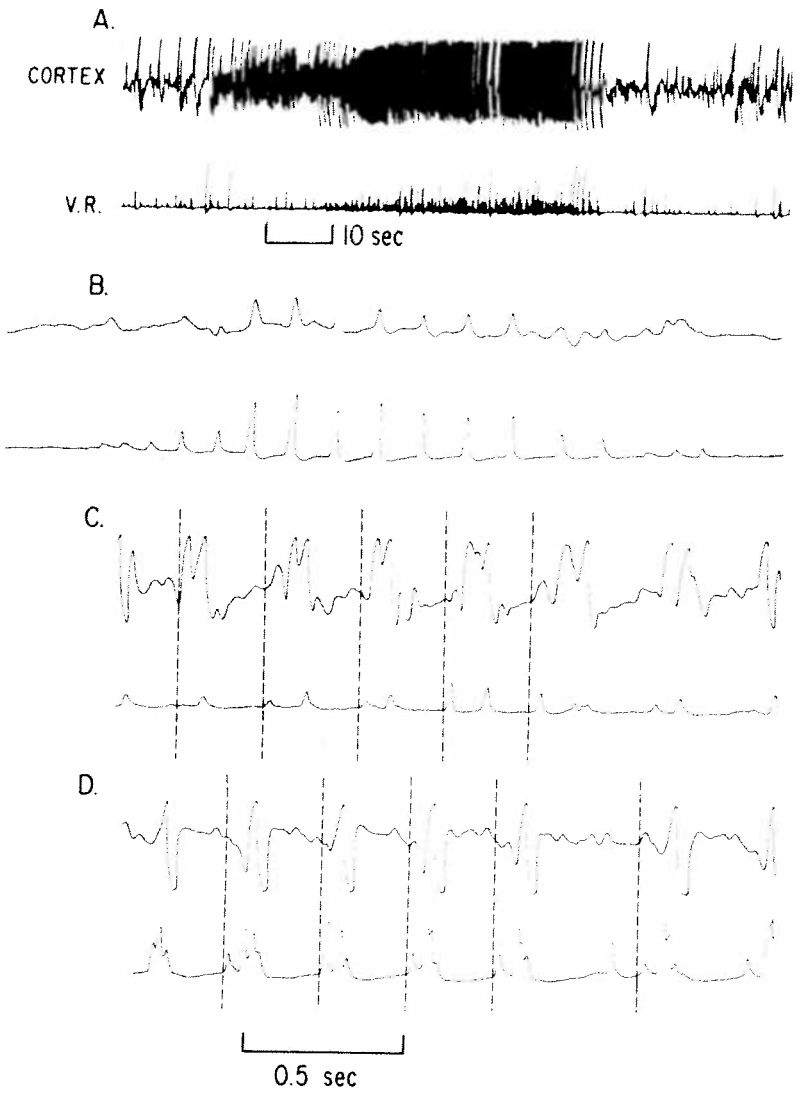

FIG. 2. Paroxysmal activity recorded simultaneously in the motor cortex representation of lumbar spinal cord and the (contralateral) L7 spinal ventral root. Recording on polygraph by EEG amplifiers. Cat rendered comatose by bilateral electrolytic lesion of midbrain reticular formation. **A:** Development of tonic seizure followed by brief clonic activity; seizure appearing first in cortex. **B:** Brief clonic episode, beginning in spinal cord. **C** and **D:** Clonic seizure activity. Vertical broken lines mark onset of seizure events. Note that sometimes the cortical discharge and at other times the spinal discharge occurs first. (T. Dunaway, unpublished experiment.)

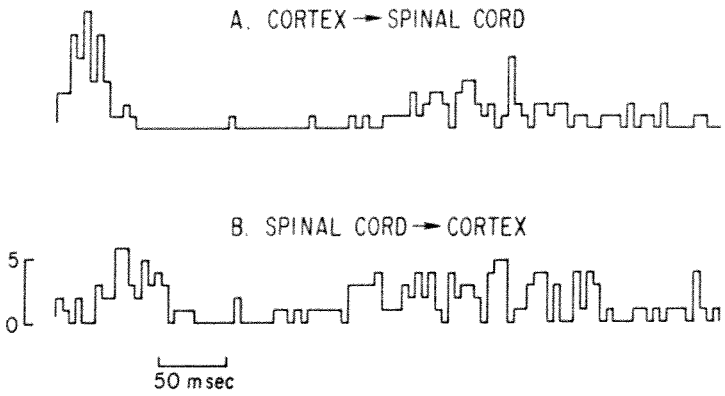

FIG. 3. Incidence distribution of clonic seizure events, similar to the ones illustrated in Fig. 2C and D. Diagrams generated by poststimulus histogram program of PDP 8E computer. **A:** Cortical clonic discharge used as "stimulus" trigger; histogram shows incidence of spinal discharges occurring after cortical discharges. **B:** Histogram of cortical discharges following spinal discharges. (T. Dunaway, unpublished experiment.)

50 msec before cortex, the velocity of conduction from the hypothetical pacemaker to spinal cord would have to exceed the conduction velocity to cortex by an improbably large margin.

EPILEPTIFORM PHENOMENA INDUCED BY PENICILLIN IN SPINAL CORD

Convulsive activity may erupt spontaneously in spinal cords treated with penicillin or they may be provoked by afferent stimulation. Gentle ruffling of hairs was remarkably effective in triggering seizures.

Spontaneous discharges conducted in spinal ventral roots may be used as an absolute diagnostic criterion of heightened excitation; in the acutely decapitate spinal cord, alpha motoneurons do not discharge action potentials when not stimulated, although they do show subliminal excitability fluctuations (see above).

Whether penicillin is administered topically or systemically, all or nearly all the motoneurons in a segment depolarize during a seizure (39). Interneurons may occasionally be subject to paroxysmal hyperpolarization and sometimes do not take any part in a seizure. Synchronization of paroxysmal activity occurs between segments and between the two sides of the cord; the shorter the distance, the more nearly perfect the synchrony (Fig. 4).

Convulsive paroxysmal activity in ventral roots is associated with electrotonically conducted negative shifts of potential in dorsal roots, which can be shown to be caused by episodic depolarization of primary afferent terminals (38). During such paroxysmal dorsal root potentials (DRPs), showers of antidromically conducted action potentials are also recorded,

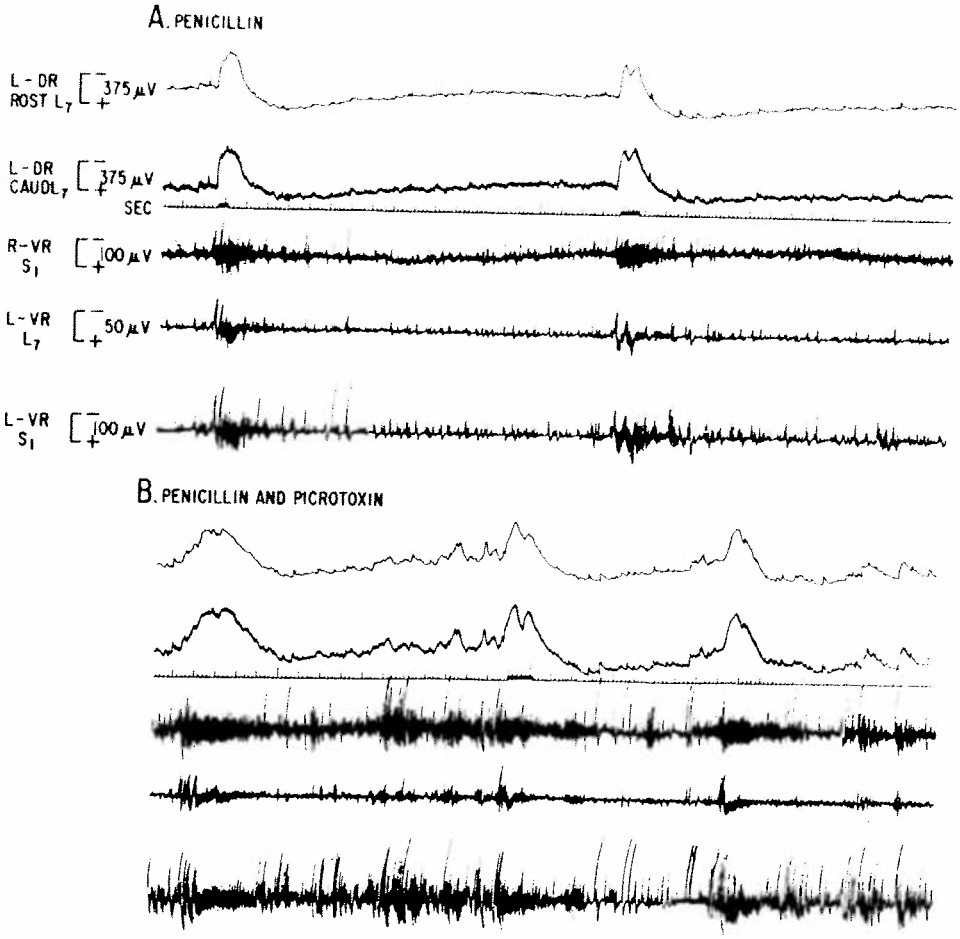

FIG. 4. Seizure activity recorded simultaneously in two dorsal root (DR) filaments, in L7 ventral root (VR), and in S1 VR of same and contralateral sides of high spinal cat treated with convulsant dose of penicillin. Ink-writer recordings by polygraph, direct coupled amplification for DR, and condenser-coupled amplification of VR discharges. (E. Lothman, unpublished experiment.)

which may be analogous to the spontaneous antidromic impulses reported to occur in thalamocortical fibers (26) and in motor axons in the phrenic nerve (42) when the terminal region is treated with penicillin. Paroxysmal DRPs are not suppressed by picrotoxin (Fig. 4).

During interictal convulsive discharges, one may record monophasic positive or diphasic positive-negative wavelets from the dorsal surface of the spinal cord. During prolonged ictal activity, the potential of the cord dorsum shifts in the negative direction (37). This is in contrast to the classic afferent-evoked negative DRP (6,34), which is associated with a positive

cord dorsum potential (20); but it is similar to the negative shift of the potential recorded during prolonged afferent tetanic stimulation (36) from the dorsal surface of spinal cords not seized by convulsions.

In motoneurons of the spinal cord, interictal discharges are associated with paroxysmal depolarizing shifts, tonic seizures with protracted de-

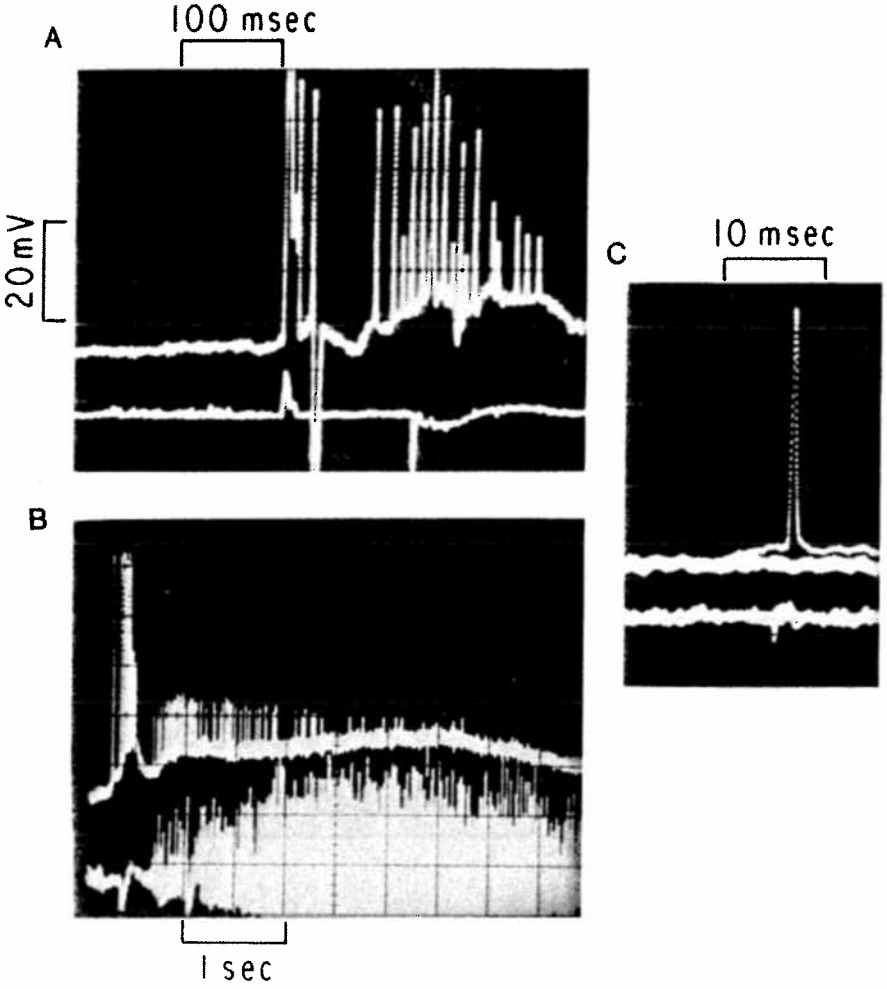

FIG. 5. Onset of tonic convulsive activity of motoneurons and of the ventral root of their segment. **A** and **B:** Same recording, played back from tape twice and recorded on a storage oscilloscope on different time bases (see time calibrations). **C:** From another cell. *Upper trace,* intracellular recording, amplification identical in **A, B,** and **C**; *lower trace,* electrical activity of ventral root. Note unusually low threshold for initial spike discharge, variable apparent threshold for subsequent action potentials, and absence of afterhyperpolarization. Note also that initially spikes are of normal amplitude but later vary irregularly.

polarization, and clonic activity with membrane oscillations synchronized with the population discharge (39). Paroxysmal depolarizations may remain subliminal, may trigger spikes sometimes in high frequency bursts, and sometimes may inactivate impulse activity. The spike potentials recorded from ventral horn cells during paroxysmal activity may have abnormally variable amplitudes (Fig. 5). Abnormal spikes may reveal anomalous membrane properties. The impulses may also be generated at a variable distance from the site of recording and may not be conducted to the site of recording. Invasion of the cell soma may be prevented by the drastic lowering of the input resistance of the cell (19). Action potential may be triggered at an unusually distant site by the intense current associated with the paroxysmal depolarization of the somadendritic membrane. The customary afterhyperpolarizations of soma spikes may also be shunted by the breakdown of membrane resistance. During seizure events, high frequency discharge of spike potentials of normal amplitude and configuration may be recorded from motor axons with intracellular electrodes (39).

PRESENT STATE OF THE SEARCH FOR A MECHANISM OF PENICILLIN-INDUCED SEIZURES

Eventually, an explanation will have to be sought for the action of all epileptogenic agents. In the meantime, it would be a major step in the right direction if any one of them would be clearly understood. Penicillin and pentylenetetrazole are probably the most investigated two convulsants, yet there is no consensus concerning the mechanism of action of either. The following is a brief synopsis of some of the theories concerning penicillin which have received attention in recent years with arguments for and against their validity.

The Potassium Hypothesis

There is no doubt that sufficient quantity of potassium ions introduced from an exogenous source into the extracellular fluid of central gray matter can cause convulsions (23). At issue, however, is the role of endogenous potassium in causing either toxic or traumatic epilepsies (40). As far as penicillin is concerned, there is no experimental support for the theory (38,43). Even though potassium does accumulate in extracellular fluid during seizures, its rise tends to follow rather than lead the discharge in ventral root. Furthermore, penicillin does not seem to impair the clearing of potassium from extracellular fluid (35,38). Cardiac glycosides, however, are known to impede the active reuptake of potassium into cells. If there is a drug that induces convulsions by causing the accumulation of K^+, it should be digitalis and its derivatives. We (12) have indeed found that after the administration of digitoxigenin, the clearing of elevated $[K^+]_0$ was retarded,

and its "resting" level was increased in the spinal cord. Seizures erupted from $[K^+]_0$ levels, which varied widely, and not from a definable threshold level, and usually at K^+ concentrations which untreated spinal cords could readily reach without triggering seizures. As with penicillin, an intense rise of potassium occurred after, not before, the appearance of convulsive discharges.

While the above observations suggest that in the case of seizures induced by both penicillin and digitoxigenin, the extracellular accumulation of potassium was a consequence and not a cause of the seizure discharge, it is nevertheless possible that, once accumulated in excess, $[K^+]_0$ may influence the patterning of convulsive activity. Excess $[K^+]_0$ might have an influence on the release of transmitter from presynaptic terminals (11,41) and may also contribute to the depolarization of postsynaptic membranes. These effects may be small compared to other influences buffeting the cell (36).

Penicillin and Resting Membrane Resistance

Either an increase or a decrease of membrane resistance could lead to phenomena resembling seizures. Increased resistance of the resting membrane (reduced leak current) would enhance the electrotonic spread beyond synaptic regions of potential changes caused by transmitter agents. It may also cause repetitive firing in the wake of single impulses (4). Reduced membrane resistance could lead to depolarization and hence to enhanced excitability.

Increased resting membrane resistance was indeed reported after treatment with penicillin of a number of invertebrate excitable cells (2,3,29). In spinal motoneurons, however, resting membrane resistance appeared unchanged when it was compared to the untreated control state and after penicillin administration measured in the seizure-free intervals (19). The expected enhancement of monosynaptic excitatory postsynaptic potentials (EPSPs) was also not observed (14,19). Admittedly, a small change could have remained undetected in these experiments; it would not, however, explain the violent convulsions.

Membrane Instability or Negative Resistance

Pacemaker activity and spontaneous burst-generation of molluscan neurons was attributed to voltage- and time-dependent nonlinearities of the current-voltage function of the cell membrane by several teams of investigators (25,52,57). Treatment with pentylenetetrazole causes the appearance of irregularly recurrent episodic depolarizing shifts in nonpacemaker neurons and enhanced pacing and bursting in pacemaker cells (8,9). Although the pentylenetetrazole-induced voltage shifts differ in several important ways from the pacemaker activity of normal cells, they neverthe-

less appear to be generated by a negative slope-resistance region in the steady-state current-voltage curves induced by the convulsant drug in cells which normally do not have this characteristic (15,18).

Schwindt and Crill (51) recently reported that in the penicillin-treated spinal cord, some but not all motoneurons show negative resistance regions of the current-voltage function investigated by the voltage clamp technique. Such an observation could be reconciled with several unrelated observations. Pentylenetetrazole-induced paroxysmal depolarizations can also be provoked by brief depolarizing pulses, as well as by excitatory synaptic potentials (18). Thus the convulsive potentials in motoneurons could be triggered by reflex excitatory input. Furthermore, it may be inferred, although it is not experimentally confirmed, that during the plateau of the pentylenetetrazole-induced voltage shift, there should be a reduced apparent input impedance, as was indeed found in the penicillin-treated cord (19) and cortex (1). In this respect, membrane instability would be indistinguishable from an exaggerated EPSP.

There are, however, some experimental observations that are difficult to reconcile with the notion that inherent instability of the membrane is the basis of the paroxysmal depolarizations induced by penicillin. In Aplysia neurons, Pellmar and Wilson (45) found no effect on excitability and current-voltage functions, even when penicillin was applied in concentrations greatly in excess of that required to affect synaptic functions (see below). Even with pentylenetetrazole, synaptic effects were seen at a concentration five times lower than that needed to induce negative resistance region in the current-voltage function (46). The drugs may affect Aplysia cell differently from cats. In the case of neurons in mammalian nervous systems, observations conflict concerning the triggering of paroxysmal potential shifts in individual cells by injecting current through intracellular electrodes. If membranes were unstable because of a negative resistance characteristic, this should be easily achieved (18).

Kao and Crill (31,32) report that paroxysmal depolarizing shifts can indeed be triggered after penicillin treatment; but it appears that complex, double-step currents had to be used, and even these were not always successful. During paroxysmal activity, it may be difficult to distinguish a triggered depolarization from a spontaneous one, unless discharges in ventral root are concurrently recorded to monitor the behavior of the neuron population. In the experience of our laboratory, it is difficult or impossible to trigger a paroxysmal wave in a motoneuron when there is no simultaneous intercurrent discharge in the motoneuron pool (19,39). Other investigators (1) report similar failure in cortical penicillin foci. Furthermore, Schwindt and Crill (51) found nonlinearities in the current-voltage functions of some of the motoneurons in spinal cords not treated with penicillin. Therefore, to make a convincing case, even though these are technically very difficult experiments, it will be necessary to render statis-

tically valid proof that penicillin treatment has altered the excitability characteristics of these cells.

Penicillin may cause instability of presynaptic terminals instead of postsynaptic membranes. The resulting burst-discharges would amplify transmitter output by a very large factor. Repetitive discharges at the nerve terminal should be conducted antidromically into dorsal roots. Unfortunately for this version of the theory, the antidromic bursts known as the dorsal root reflex are depressed rather than enhanced by penicillin (17,38).

Penicillin and Postsynaptic Inhibition Mediated by GABA

There are several concordant reports indicating that penicillin interferes with the inhibitory effects of gamma-aminobutyric acid (GABA) (10,13). This may or may not be the decisive factor in the generation of seizures in the brain. In the spinal cord, the role of GABA in postsynaptic inhibition is uncertain; and postsynaptic inhibition is unimpaired by penicillin (17,39). Although recurrent inhibition was somewhat depressed by penicillin, the effect was not impressive (39).

However, GABA is considered by several authors to be the mediator of presynaptic inhibition in the spinal cord. Possible interference with this function is the theory to be discussed next.

Penicillin, Negative DRP, and Presynaptic Inhibition

According to a report by Davidoff (16,17), penicillin depresses the negative DRPs evoked by afferent stimulation in the spinal cord of frogs (16) and cats (17). This observation would put penicillin into the same class of convulsant as picrotoxin and bicuccullin, sharing with them the blocking effect of postsynaptic inhibition in brain and presynaptic inhibition in spinal cord.

Disconcertingly, in our hands (38) penicillin did not suppress afferent-evoked negative DRPs, nor the excitability change attributable to primary afferent depolarization, nor indeed the reflex inhibition commonly interpreted as presynaptic. While the amplitude of DRPs remained unchanged, their rate of rise was undoubtedly depressed, as was the antidromic discharge known as the dorsal root reflex. We found two possible reasons for our findings (38) to differ from those of Davidoff (17). During convulsions, spontaneous paroxysmal DRPs occluded the afferent-evoked DRP; and, especially with AC-coupled recording and electronically computed averages, such occlusion could be mistaken for depression. More important, in the presence of an anesthetic dose of pentobarbital, penicillin became a very effective depressant. How the two drugs interact is not clear, but it will be recalled that pentobarbital in moderate doses augments and in high doses depresses the negative DRP.

These observations seemed to rule out blockade of presynaptic inhibition as an explanation of the convulsant action of penicillin but maintained the impression of interference with some aspect of presynaptic function of the drug. This impression was reinforced by the somewhat paradoxical finding of depressed posttetanic potentiation by convulsant amounts of penicillin (33). Because of this persistent belief of presynaptic involvement, we decided to renew our investigation of the effect of penicillin on the negative DRP.

As a point of new departure, we took the observation that in the penicillin-treated spinal cord the best stimulus to provoke a seizure is the gentle but persistent ruffling of hairs. We argued that testing by single shocks may not reveal a defect which is manifest only during prolonged stimulation. Instead of the customary isolated volleys, we are therefore recording DRPs during and in the wake of prolonged repetitive stimulation. There is no posttetanic potentiation of negative DRPs which, instead, are subject to posttetanic fatigue (6,30). In some but not all experiments, posttetanic depression of afferent-evoked DRPs appeared greatly aggravated by penicillin treatment. We are in the process of investigating whether the exaggerated fatigue of DRPs is in any way correlated with the generation of seizures (C. Gray and G. G. Somjen, *work in progress*).

Blockade of Chloride Ionophores by Penicillin

According to Hochner et al. (29), the enhanced membrane resistance (i.e., reduced leak conductance) of crustacean muscle and the depression of GABA-mediated inhibition could both be explained by a single mechanism if penicillin blocked not the GABA-receptor but the carrier of chloride ions in the membrane. Pellmar and Wilson (45) report that in neurons of Aplysia, penicillin suppresses all chloride-dependent synaptic processes, regardless of transmitter. Penicillin seems to share this property with several other convulsant drugs, including pentylenetetrazole (46; see also chapter by Carpenter, *this volume*).

Impairment of the chloride conductance in the mammalian nervous system could cause suppression of inhibitory postsynaptic potentials (IPSPs) and repetitive discharge at presynaptic terminals (for this mechanism, see ref. 4). Iteration of spiking was reported at motor nerve terminals under the influence of penicillin (42,49); but at primary afferent terminals in the spinal cord, the reflexive discharge (DR reflex) is depressed rather than enhanced (38) (see also previous section). Whereas GABA-mediated inhibitory responses in brain are subject to depression by penicillin, the supposedly chloride-dependent but glycine-mediated spinal IPSPs are not. Yet the negative DRP, upon which penicillin has an effect under certain conditions, (see above) may in part be dependent on chloride ions (5).

PROSPECTUS

In sum, here are six characteristics in search of an explanation.

1. Administered either topically or systemically, penicillin induces convulsive activity in the spinal cord, which is synchronized over several segments. In a convulsing segment, all or nearly all alpha motoneurons but not nearly all interneurons depolarize. The convulsive dose is not higher for cord than for cortex. Paroxysmal discharges in spinal segments sometimes drive convulsive activity in the brain.

2. Paroxysmal depolarization of motoneurons is accompanied by a precipitous decline of membrane resistance. In seizure-free intervals, the resting membrane retains its normal impedance and voltage.

3. Monosynaptic EPSPs and disynaptic IPSPs evoked in spinal cord by synchronized afferent volleys are not affected by penicillin.

4. Presynaptic inhibition and the amplitude of negative DRPs evoked by single synchronous afferent volleys are unchanged after penicillin. The rate of rise of the negative DRP is usually reduced, and posttetanic fatigue of the DRP is aggravated. The dorsal root reflex is invariably depressed by penicillin, as is posttetanic potentiation of the monosynaptic reflex.

5. During convulsions, intraspinal primary afferents depolarize. This effect is more noticeable in afferent fibers of muscle nerves than in cutaneous fibers. Frequently but not invariably, paroxysmal DRPs begin earlier than seizure activity of motoneurones. Paroxysmal primary afferent depolarization gives rise to showers of antidromic impulses in sensory fibers.

6. Potassium activity rises in extracellular fluid during seizures, more so in ventral horn than in intermediated or dorsal gray matter. Paroxysmal potassium responses always trail behind, never lead, seizure activity. The release of potassium ions associated with evoked neural responses is also enhanced by penicillin, more noticeably in ventral horn than elsewhere.

Although the patterning of seizures induced by penicillin in high spinal preparations resembles epileptiform convulsions seen in intact animals, there is one important difference. Grand mal attacks can readily be provoked by electric stimulation of otherwise perfectly normal brains. The spinal cord requires a convulsant drug to be able to generate a full ictus. The seizure activity evoked by electric stimulation of cords not treated by drugs (21) is only rudimentary by comparison. It would seem almost that penicillin introduces into the spinal cord an element already present in the healthy forebrain, albeit in a latent state.

The conclusion is almost inescapable: seizure activity requires self-reexcitation. Tonic convulsions seem to be the result of unbridled positive feedback. In the oscillations that drive clonic beating, there must be an element of negative feedback with a significant delay in the feedback loop. A theory of cortical seizure activity (1) is based on recurrent excitation of

pyramidal cells. In spinal cord, a recurrent excitatory pathway is not believed to exist, but only recurrent disinhibition (56). Accordingly, antidromic stimulation of the ventral root of penicillin-treated spinal cords does not initiate seizure activity (E. W. Lothman, *unpublished observation*). The local circuits providing positive feedback may of course exist in the concentration of short axon interneurons in the intermediate gray matter; these may provide the drive for motoneurons of the ventral horn. Feedback need not be neural, however, but could be biochemical. Chemical feedback was the basic idea in the potassium theory, which, as we saw earlier, is currently losing ground.

Almost all the facts relating to penicillin-induced spinal seizures could be tied together with the least strain of logic by the following assumptions. The primary convulsive event may be inward current welling up simultaneously in many afferent terminals. Paroxysmal DRP may be a manifestation of such current. If carried by both Na^+ and Ca^{2+} ions (see also chapter by Heinemann et al., *this volume*), it would bring about the release of a massive amount of transmitter, with the consequent widespread and synchronous depolarization of motoneurons, the drop in their membrane resistance, and the release of large amounts of potassium from both pre- and postsynaptic sources. A cause for the synchronous inward current of presynaptic terminals remains to be found. The theory would be helped greatly by the discovery of a metabolite, released into extracellular space in toxic amounts under the influence of penicillin, and in smaller amounts by nerve excitation. An amino acid with a nonselective effect on membrane permeability could fill the role.

We know that during convulsions, the demand for oxidative energy greatly exceeds that which normally is consumed at equivalent concentrations of potassium (35). The excess energy may be needed in part to pump back potassium through a membrane that has become too permeable for potassium. Additional extra energy may be spent in oxidizing the postulated toxic metabolite.

The author knows that the reader knows that the key elements postulated for this theory are not yet demonstrated experimentally. Still, the theory could organize observed facts, which otherwise seem disparate.

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