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Physiological basis of pathophysiological brain rhythms

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Abstract. Focal epilepsy may be induced acutely in the brain *in vivo* by measures which reduce inhibition or enhance excitation. Athough the various models involve different mechanisms causing the epilepsy, their epileptiform discharge patterns vary only little. Intracellular analyses *in vivo* and *in vitro* reveal that the cellular hallmark of epileptic discharge, the paroxysmal depolarization shift, is followed by a giant hyperpolarization. The latter is comprised of several, overlapping, components with different durations, including calcium dependent potassium currents and GABA dependent inhibitions. Relative reduction of one inhibitory component is compensated by other inhibitory components. In epilepsy caused by reduction of GABAergic inhibition, the absolute duration and amplitude of GABAergic inhibition may even be increased in comparison to the responses following afferent stimulation under control conditions since the excitatory drive of the paroxysmal discharges on the interneurons is strongly increased. In some interictal discharge patterns, the enhanced inhibitions within the focus determine the refractory periods of the focus. The latter is paced by neurons from the perifocal area which show a shorter inibition associated with the interictal epileptic event. The discharge pattern of the focus may switch to other patterns, either spontaneously, or as entrained by external stimulation. Such changes are caused e.g. by progressive potassium accumulations in the extracellular space with critically small intervals of the epileptic events. It is concluded that the epileptiform discharge patterns reflect intrinsic properties of the brain, and do not very well reflect the mechanism of action of the epileptogenic model. The brain is thus equipped with inherent mechanisms which favor rhythmic epileptiform discharges under certain conditions.

Review

Key words: epilepsy, inhibition, pacemaker, inhibitory surround, brain rhythm

INTRODUCTION

Since the invention of the electroencephalography, brain rhythms have fascinated the researchers. For a long time they were regarded as an indication that the brain was not active (idling rhythms) (Chen and Hallett 1999, Schurmann and Basar 1999). A typical example is the occipital alpha rhythm. In recent years the general interest and the possible physiological significance for the binding problem have revived the interest in brain rhythms (Singer 1999a,b).

Rhythmic activity is also a characteristic feature of some brain diseases. Thus, epilepsy is not only characterised by spikes and sharp waves in the EEG, but also by rhythmic brain activity. Indeed, often the rhythmicity of the electrographic events is more characteristic for the epileptic nature of the discharges than their sharpness or the shape of the singles events (Hefter et al. 1992, Dorn and Witte 1993, Hefter et al. 1994). There are some typical epileptic patterns for certain epilepsies, for instance, the three per second discharges in primary generalized epilepsy. However, generally the epileptiform discharge patterns are rather independent from the cause of the epileptic disorder. This indicates that the epileptiform discharge pattern is not caused directly by the epileptogenic lesion; instead the epileptogenetic lesion triggers an inherent function of the normal brain. Thus, epileptic discharges rather than constituting pathologic phenomena alone may in fact disclose some basic properties of the brain.

It is generally accepted that epilepsy may derive from an imbalance of excitation and inhibition. When substances known to reduce GABAergic inhibition like penicillin or bicuculline are applied locally to the brain they cause a focal epilepsy (Gutnick et al. 1982, Witte et al. 1994). A similar effect is obtained with substances which enhance excitations. A typical example of the latter is the reduction of magnesium which increases NMDA dependent excitations (Westerhoff et al. 1995). Intuitively one therefore often expects that epileptiform discharges are associated with decreased inhibitions in the epileptic focus. In contradiction to this, one often finds very strong inhibitions in these areas following epileptiform discharges as well as subsequent to stimulation of afferents to the brain.

This apparent discrepancy will be analyzed in the following paragraphs using classical models of acute epilepsy *in vivo* and *in vitro*.

METHODS

Experiments on brain slices (Domann et al. 1989, 1991a,b, 1993) were performed on hippocampal slices of Wistar rats (250-400 g body weight). Under ether anesthesia, the rats were decapitated and the hippocampi were dissected free. Transverse slices of 400 m were cut on a tissue chopper and immediately transferred to the recording chamber. There the slices were equilibrated with standard artificial cerebrospinal fluid (standard ACSF, containing: 124 mM NaCl, 26 mM $NaHCO_3$, 5 mM KCl, 2 mM $CaCl_2$, 2 mM $MgSO_4$, 1.25 mM NaH_2PO_4, 10 mM glucose, equilibrated with 95% O_2 - 5% CO_2, pH 7.4) for at least one hour. Then epileptiform activity was induced by either adding 3.4 mM penicillin (penicillin ACSF) or 100 M bicuculline (bicuculline ACSF) to the standard ACSF or by omitting $MgSO_4$ (Mg-free ACSF). Intracellular recordings were obtained from CA1 pyramidal cells. The recording electrodes were filled with 2 M KCH_3SO_4. For orthodromic stimulation, a bipolar stimulation electrode was placed in stratum radiatum of the CA2/CA3 region. Signals were stored on FM-tape for off-line analysis.

Experiments on the neocortex *in vivo* (Dorn and Witt 1993, 1995, Witte 1994, Witte et al. 1994, Bruehl and Witte 1995, Bruehl et al. 1995, 1998a,b) were carried out on male Wistar rats weighing 250 g to 400 g. The animals were anesthetized with halothane (2.5 Vol.% during operation, thereafter reduced to 0.5 Vol.%). After tracheotomy, the animals were placed into a stereotaxic frame, paralyzed by repeated intraperitoneal injections of suxamethonium or d-tubocurarine and ventilated artificially. The ECG was continuously monitored. Animal temperature was kept constant at 36.5°C. In some experiments ventilation was controlled by repetitive determinations of pO_2, pCO_2 and base excess in blood samples of the left iliac artery.

Following trephination of the bone over the motor cortex the dura was dissected. A glass-capillary (diameter 1.5 mm) filled with agar-agar dissolved in artificial cerebrospinal fluid was placed onto the brain for recording of epicortical DC potential. A similar capillary placed onto the frontal nasal bone served as reference electrode both for DC potential and intracellular recordings.

For eliciting focal epileptiform activity small droplets of penicillin (20,000 or 50,000 IU/ml CSF) were applied onto the surface of the cortex. The penicillin solution was applied with microsyringes or by pressure ejection

through small micropipettes with tip diameters broken down to 1-10 m. Intracellular recordings were carried out after a stable focus had developed which did not change its characteristics as judged from frequency of epileptiform events and shape of the epicortical DC potential changes.

Intracellular recordings were obtained using glass microelectrodes with resistances ranging between 100 MΩ and 300 MΩ when filled with 2 mol/l potassium-methylsulphate. Microelectrodes were inserted into the cortex perpendicularly to the surface. For impalement of neurons a stepping motor microdrive was used (Nano Stepper). The position of cells within the cortex was estimated from the scale of the microdrive. A high impedance microelectrode amplifier (Polder SEC 1 L/D or DA-2D) equipped with a bridge circuitry was used for recording membrane potential and for intracellular current injection. Recordings were obtained from neurons in all cortical layers. Epicortical stimuli were applied through silver screw electrodes mounted immediately rostrally and caudally of the burr hole. They were applied from an isolated stimulator, lasted between 10 s and 100 s and had amplitudes of 10-30 V.

RESULTS AND DISCUSSION

Inhibition in epilepsy

Figure 1 shows a typical response of a hippocampal CA1 neuron *in vitro* to stimulation of the Shaffer collaterals under control conditions. This causes an initial excitation topped by action potentials and followed by a subsequent inhibition which is shown on a different time scale in the lower trace. Following superfusion of the brain slice with a penicillin containing cerebrospinal fluid the response to stimulation dramatically increased, giving rise to a classical paroxysmal depolarization shift. The events are depicted on a compressed timescale in other lower trace: the paroxysmal depolarisation is followed by a paroxysmal hyperpolarization.

The reason for this increased inhibitory response is depicted in Fig. 2. In the epileptic focus not only excitatory neurons show paroxysmal deposition shifts, but also inhibitory ones as shown here for typical fast spiking interneurons (Domann et al. 1991a). The paroxysmal excitation of interneurons recruits massive inhibitory recurrent and feed forward inhibitions in the excitatory neurons.

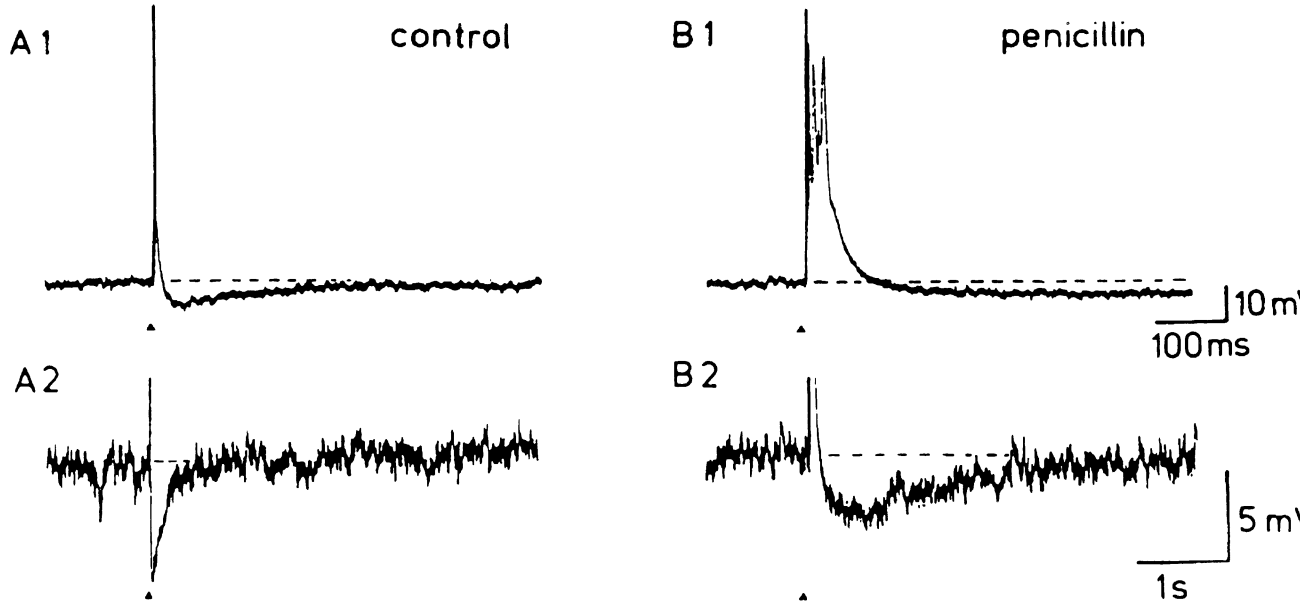

Fig. 1. Intracellularly recorded responses of hippocampal CA1 neurons *in vitro* to afferent stimulation (triangle) under control conditions (A) and during superfusion of the preparation with penicillin containing solution (B). Rows 1 and 2 show the same recordings with different time scales. Superfusion with penicillin induced paroxysmal depolarisation shifts followed by strongly enhanced inhibitions.

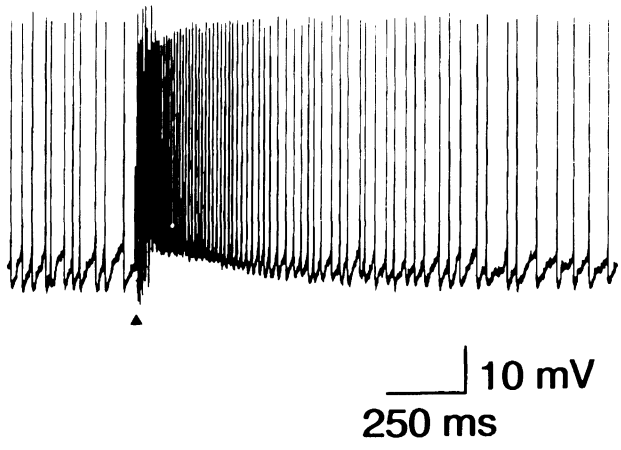

Fig. 2. Intracellular recording from fast spiking interneurons from the somatosensory cortex of the rat *in vivo*. The recording was obtained from the center of a penicillin induced epileptic focus. Note paroxysmal discharge of the interneuron.

In several experimental approaches both *in vivo* and *in vitro*, several components could be identified which participate in the generation of the giant inhibitions following the paroxysmal depolarization shifts (Domann et al. 1989, 1991b, 1993, 1994, Witte 1994). This is summarised in a diagram in Fig. 3. Since the paroxysmal depolarization shifts are amplified by calcium currents (Speckmann et al. 1986, Witte et al. 1987, Straub et al. 2000), they are followed by a calcium dependent potassium current lasting more than two seconds. In addition, GABAergic inhibitions participate in the generation of these huge inhibitions. Penicillin induced paroxysmal depolarization shifts are followed by a $GABA_B$ dependent potassium current lasting in the order of one second. Furthermore, a $GABA_A$ dependent chloride current is activated under these conditions. This is very prominent in the border region of a penicillin focus *in vivo*. With penicillin superfusion of brain slices, the $GABA_A$-dependent inhibitions are massively enhanced and prolonged compared to the normal responses to stimulation of the Shaffer collaterals. This is due to the fact that even if a certain percentage of GABA-ergic receptors is blocked by penicillin, the proportion of GABA-ergic receptors recruited and the time course of recruitment are massively increased when compared to control conditions. This results in a relative imbalance of excitation and inhibition with a giant increase of excitations but also a massive increase of GABAergic inhibitions. In addition to these components, a fast calcium dependent potassium current participates in the generation of the inhibitions following the paroxysmal depolarization.

These observations show that there is not a simple dichotomy of excitation and inhibition (Prince 1999): there is a cascade of several different, overlapping, types of inhibitions in the brain. If one of these is diminished or even abolished, a compensatory increase of the others is likely. This also explains, why a single stimulations of such epileptic brain tissue will not automatically generate seizure activity. It has indeed been shown that in patients with focal epilepsy, epicortical magnetic stimulation with single stimuli only very rarely induce seizures (Classen et al. 1995, Schulze-Bonhage et al. 1999, Menkes and Gruenthal 2000). Transition from interictal to ictal discharge patterns must thus involve special mechanisms.

If the epilepsy is induced by altering another component of the brain network this only has some subtle effects on the duration of the paroxysmal depolarization shifts. With penicillin containing cerebrospinal fluid, the paroxysmal depolarizations lasted between 30 ms and 60 ms (duration measured at half amplitude; average: 40.2 ± 9.2 ms, $n = 89$), and with Mg-free cerebrospinal fluid between 35 ms and 90 ms (average 54.2 ± 21.7 ms, $n = 25$). With bicuculline containing cerebrospinal fluid, the longest paroxysmal depolarizations occurred: they lasted between 55 ms and 120 ms (average: 76.3 ± 14.7 ms,

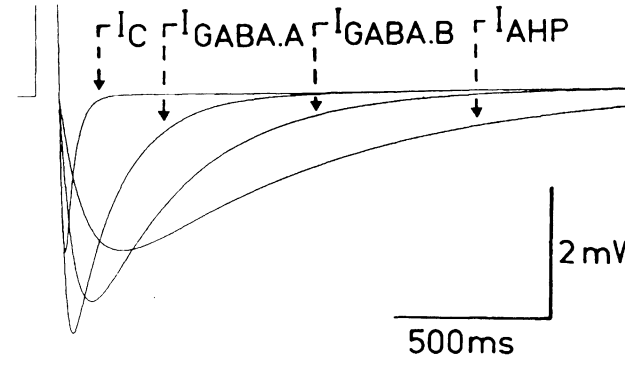

Fig. 3. Schematic drawing of the components which comprise the enhanced inhibition following paroxysmal depolarisation shifts induced by penicillin in the neocortex or hippocampus. The inhibition comprises a fast calcium-dependent potassium current (I_C), a $GABA_A$-dependent component associated with increased chloride conductance ($I_{GABA.A}$), a $GABA_B$-dependent component which is not calcium dependent and is associated with an increased potassium conductance ($I_{GABA.B}$), and a long lasting calcium dependent potassium conductance (I_{AHP}).

$n = 36$). Resting membrane potential and input resistance of the neurons did not change significantly in any of the above mentioned epileptogenic cerebrospinal fluids. Similarly there are small differences between the components of the afterhyperpolarization. However, the general pattern remains unaltered.

Pacemakers of epileptic activity

The epileptic event is not only characterized by its sudden onset and end, but also by its rhythmicity. Experiments *in vivo* revealed that these discharge patterns are governed by the giant inhibitions following the paroxysmal discharges. Figure 4 shows a recording from a neuron in the center of a penicillin focus *in vivo*. These neurons have a very high resting potential, and are usually silent in between subsequent paroxysmal discharges. The interval between subsequent discharges varies to some extent and is not related to the membrane potential of the neuron. The subsequent paroxysmal discharge therefore appears without any preceding warning from a very negative potential. A comparison of such recordings with those shown above explains the high resting potential as well as the silence of the neurons between subsequent discharges: The inhibition in the focus outlasts the duration of the interval between subsequent discharges.

These recordings indicate that the pacemakers for this epileptic pattern cannot be localized within the center of the focus. The pacemaker cells must show activity before the slow inhibitions following a paroxysmal discharge have vanished. Such a situation would be expected in the so-called inhibitory surround of the epileptic focus (Prince et al. 1967, Elger and Speckmann 1983, Witte et al. 1994, Bruehl and Witte 1995, Bruehl et al. 1995, 1998a, b), the inhibitory connections of neurons span a wider brain area than the excitatory ones. Therefore, the focus is surrounded by an area in which

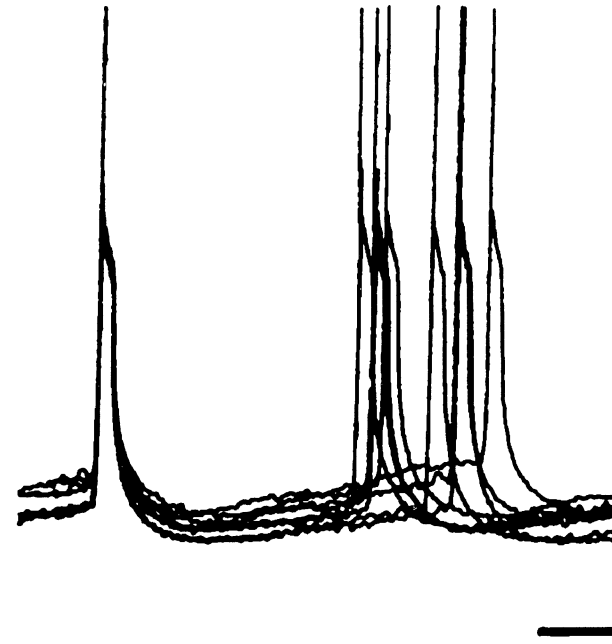

Fig. 4. Intracellular recording of penicillin-induced paroxysmal depolarisation shifts in the somatosensory cortex of the rat *in vivo*. Seven pairs of successive discharges were superimposed. Note variation of intervals between successive discharges and absence of spontaneous action potentials or excitatory postsynaptic potentials in this interval. Calibration: 500 ms, 10 mV.

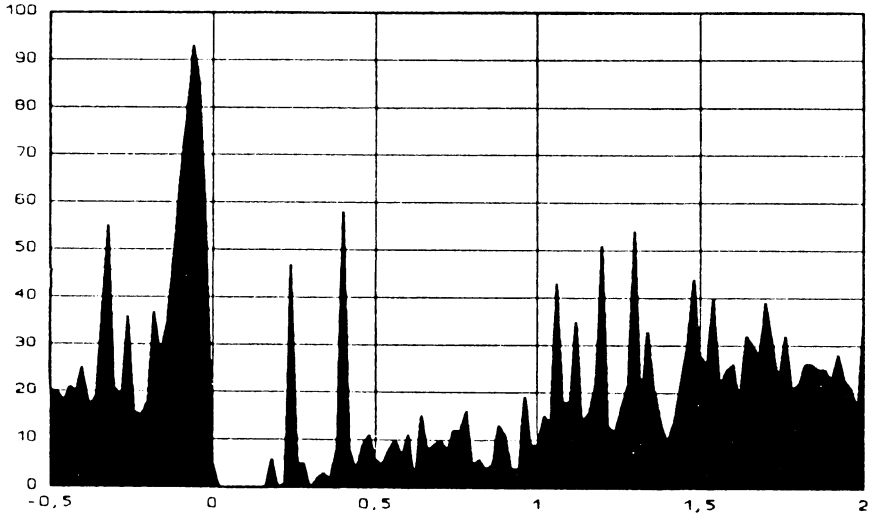

Fig. 5. Poststimulus time histogram of action potentials of neuron in the so-called inhibitory surround of a penicillin induced epileptic focus in the neocortex of the rat *in vivo*. Abscissa: time in s, 0 denotes onset of epileptiform spike in the surface EEG in the center of the epileptic focus. Ordinate: number of action potentials per bin, bin width 20 ms. Sum of 59 subsequent sequences. Note inhibition lasting about 1 s, and stochastic neuronal discharges thereafter. The backaveraging using the spike in the EEG indicates that an excitation of these neurons always preceded the spike.

the neurons display no paroxysmal discharges, but strong synaptic inhibitions. The longest component of the epileptic inhibition - the long lasting calcium activated potassium current - should not be activated in these neurons since they do not display the paroxysmal depolarisations and therefore are not strongly loaded with calcium. This is indeed found in neurons from the perifocal brain areas. They display strong inhibitions associated with the epileptiform discharges in the focus. These inhibitions last about 1 s, significantly less than the inhibition following the paroxysmal depolarisations. After the end of these inhibitions, the perifocal neurons start to discharge stochastically (cf. Kowalik and Witte 2000).

In a subset of such neurons, backaveraging of the membrane potential with respect to the spike in the EEG revealed that these neurons were active in the last 100 ms before onset of the epileptiform event. This indicates that such randomly discharging neurons may trigger the focus (Fig. 5). The interval between subsequent epileptiform events in this interictal state was thus determined by the refractory period of the neurons within the focus. The impuls to generate a new epileptiform event starts, at least in this model, from perifocal areas.

Change of discharge patterns

The epileptic focus of the neocortex *in vivo* displayed different epileptiform discharge patterns. These different patterns were called irregular, composed, regular, and ictal (Dorn and Witte 1993). Examples for these types of activity are shown in Fig. 6. The mean interspike interval length in the irregular activity was 1,990 ms ±

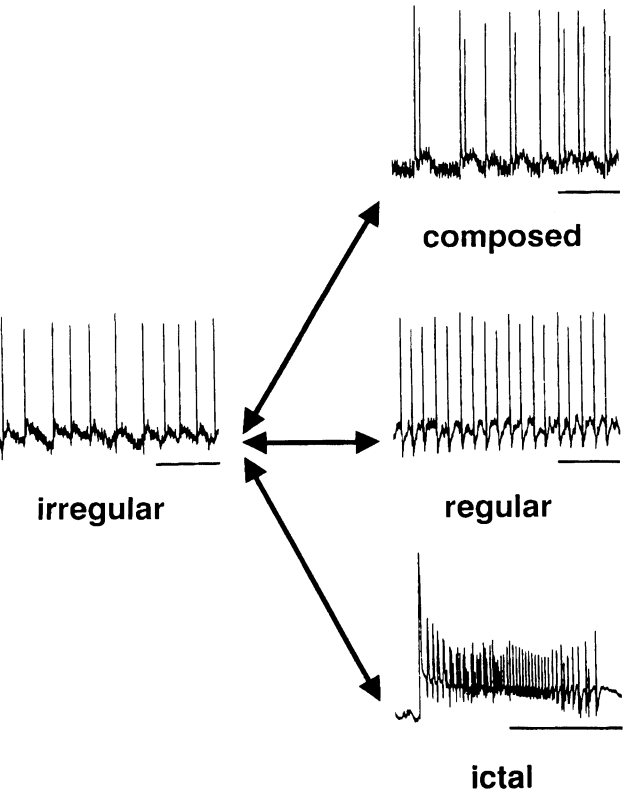

Fig. 6. Different discharge patterns induced by epicortical penicillin application in the anesthetized rat. Epicortical EEG recorded from the focal area. Possible transitions between patterns are indicates by arrows. Calibaration: 5 s.

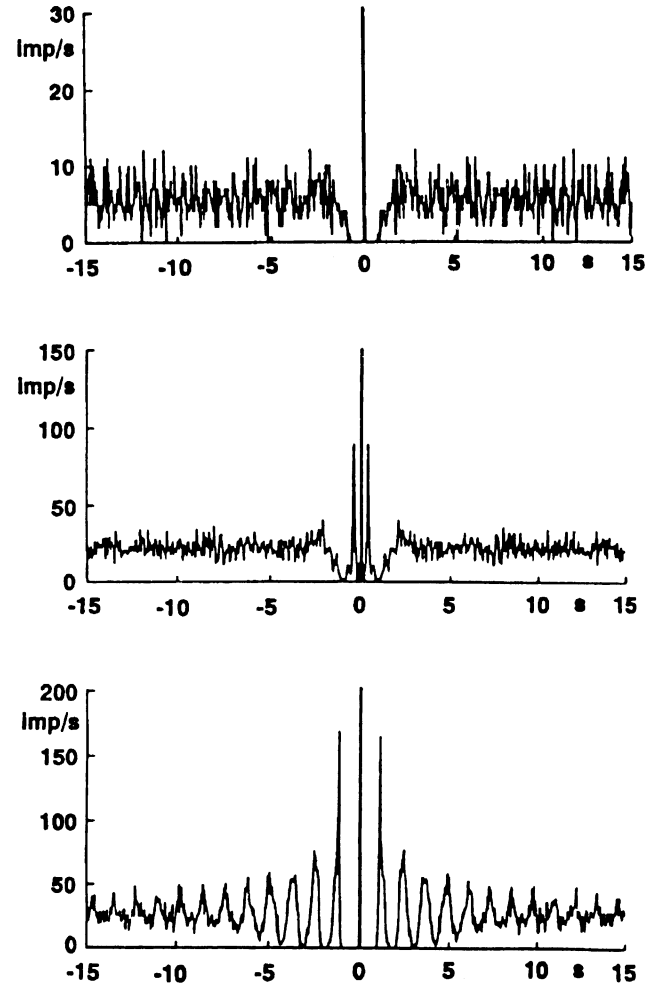

Fig. 7. Autocorrelation functions of EEG from penicillin induced epileptic focus with irregular pattern (top row), composed pattern (middle row) and regular pattern (bottom row).

560 ms (mean ± SD, duration of analysis sequence 17 min). The lengths of successive intervals varied to a great extent. In the composed pattern a long interspike interval was followed by one to three short intervals or by a further long interval. The mean length of the short intervals was 490 ms ± 100 ms, that of the long ones was 1,900 ms ± 600 ms (duration of analysis sequence 9 min). In the regular pattern the lengths of successive intervals showed only a little variation (mean interval length in the complete sequence lasting 38 min: 1,129 ms ± 230 ms). Other discharges patterns which appeared transiently were double spikes with peak to peak interval of about 50 ms and ictal discharges.

The irregular, regular and composed discharge patterns appeared within the same experiments but could clearly by differentiated. They differed in interspike interval length and spike shape. Interval histograms provided no good criterion to differentiate regular and irregular discharges. Since, however, interval length of successive spikes showed nearly no variation in the regular pattern while they varied greatly in the irregular pattern, autocorrelations are a good means to differentiate these patterns (Fig. 7). If beginning and end of the sequences were choosen on the basis of sudden changes in spike frequency and spike shape, a criterion of three or more peaks within the first 5 s with a frequency of less than 2/s and an amplitude of more than three times noise level for all peaks proved to identifiy all regular sequences in all experiments. In comparison, autocorrelations of irregular sequences were flat and never showed more than one peak within the first 5 s exceeding noise level by more 100 %. Composed patterns were identical to irregular ones, but showed an additional peak around 300 ms. The transitions between the different discharge patterns were very abrupt. A typical example is shown in Fig. 8.

In order to study the mechanisms causing the different discharge patterns, we analyzed the threshold for eliciting an epileptic event subsequent to a preceding paroxysmal discharge (Dorn and Witte 1995). This revealed an absolute refractory period of 200 ms to 300 ms followed by a relative refractory period up to 700 ms to 900 ms following onset of the conditioning spike. This is in accordance with early results which revealed an absolute refractory period of about 250 ms and reduced spike amplitudes up to 750 ms following spike onset (Prince 1965, 1968). Though determinations of spike threshold did not reveal a further drop of the threshold around 2 s, in several of the experiments it was slightly, but definitely easier to elicit spikes with intervals in the order of two seconds than those with shorter intervals. The long intervals around 2 s are in the order of the intervals with which the focus discharges spontaneously.

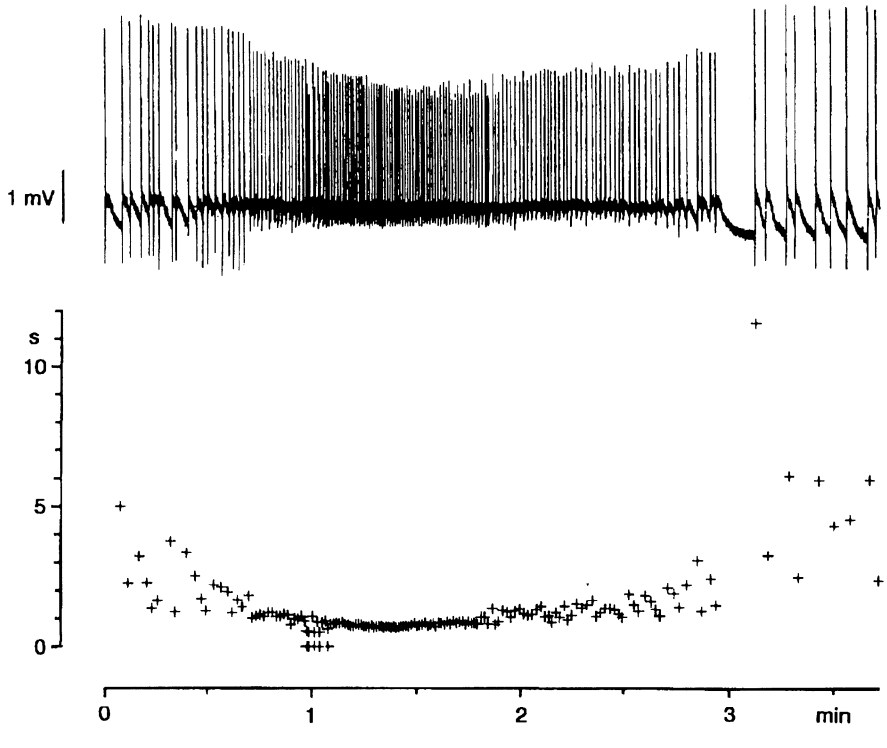

Fig. 8. Transition from irregular to regular epileptic discharge pattern in penicillin-induced focal epilepsy in the neocortex of the anesthetized rat. Top row: original EEG, bottom graph: plot of intervals of successive spikes against time. Note sudden transition between discharge patterns associated with change of spike trajectory.

Unexpectedly, it was found that pacing of the focus with external stimuli in intervals similar to those found in the regular firing pattern, favored transition to this pattern. Such a transition was associated with a diminution of spike threshold. Thus pacing the focus with a certain frequency changed the properties of the focus.

Intracellular recordings reveal a possible cause for this behavior. As pointed out above, the irregular (long interval) discharge pattern is probably governed by the slow calcium activated potassium current of the neurons within the focus. The absolute refractory period corresponds in its length to the $GABA_A$ dependent inhibitions. Very fast subsequent stimulations can therefore be expected to be ineffective. However, within a medium time window around one second the focus – and the surround – are not completely refractory any more. At the same time, - unlike stimulations with intervals of about 2 s - pacing of the focus with this frequency causes a progressive increase of the potassium baseline level in the focus: every epileptic discharge is associated with an extracellular increase of potassium, both in the focus and the perifocal surround. This redeclines with time constants of *2 s to 4 s* (Jensen and Yaari 1988, 1997, Huguenard 1998).

CONCLUSIONS

The experiments show that epileptiform discharge patterns reflect intrinsic properties of the brain, and do not very well reflect the mechanism of action of the epileptogenic model. The brain is thus equipped with inherent mechanisms which favor rhythmic epileptiform discharges under certain conditions. Whether the same rhythmic activities have a physiological role under certain conditions, or represent an alternative activity mode of oscillators which under control conditions show a different oscillatory activity remains to be investigated.

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