Evolving Concepts on the Pathophysiology of Absence Seizures

The Cortical Focus Theory

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Our main theories on the pathophysiology of generalized absence seizures have been proposed. The "centrencephalic" theory, proposed in 1954, suggested that discharges originate from a deep-seated diffusely projecting subcortical pacemaker in the midline thalamus. This concept was refined in 1991 with the "thalamic clock" theory, implying that the reticular thalamic nucleus contains the pacemaker cells for the thalamic clock, imposing its rhythm to the cortex. According to other investigators, however, the cortex seems to play a leading role. They suggested that spike-wave discharges have a focal onset in the cortex and are generalized through a rapid propagation. In the "corticoreticular" theory, postulated in 1968, spike-wave discharges are linked to the thalamocortical mechanisms that generate spindles. Rhythmic spindle oscillations generated in the thalamus are transformed into spike-wave discharges when the cortex is hyperexcitable. A 2002 study confirmed in epileptic rats that a functionally intact thalamocortical network is required for the generation of spike-wave discharges. The corticothalamic interrelationships were investigated by means of nonlinear association signal analyses of multiple spike-wave discharges. This showed a consistent focus within the perioral region of the somatosensory cortex. From this focus, seizure activity generalizes rapidly over the cortex. During the first cycles of the seizure the cortex drives the thalamus, while thereafter cortex and thalamus drive each other, thus amplifying and maintaining the rhythmic discharge. In this way the "cortical focus" theory for generalized absence epilepsy bridges cortical and thalamic theories.

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In 1941, Jasper and Kershman analyzed the electroencephalograms (EEGs) of patients with petit mal absence seizures. Seizures were characterized by an abrupt onset and termination in both hemispheres and by a high interhemispheric synchronization of spike-wave activity. Because no evidence could be found for a cortical origin, Jasper and Kershman proposed that the seizures had a subcortical origin. The putative subcortical pacemaker should project to both hemispheres simultaneously. Support for the existence of such a subcortical pacemaker came with the investigation of thalamocortical connections by Morison and Dempsey in 1942. In addition to the specific thalamocortical projection system, they demonstrated the existence of a second thalamocortical projection system with nonspecific diffuse connections, which has its origin in a relatively small thalamic area, the intralaminar nuclei of the thalamus. Single-shock electrical stimulation of these intralaminar thalamic nuclei evoked a spindlelike EEG pattern over large areas of cortex in the cat, while low-frequency stimulation elicited a "recruiting response." They further showed that this intralaminar thalamic recruiting system projects in a diffuse way to the en-

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tire cortex, but in particular to the parietal and frontal areas, over which petit mal spike-wave discharges have their maximum in patients.

These findings enabled Jasper and Droogleever Fortuyn in 1947 to establish the first experimental model of a spike-wave pattern: the thalamic stimulation model. They found that a 3-per-second stimulation of the intralaminar thalamus could occasionally produce a 3-per-second bilaterally synchronous spike-wave EEG pattern in lightly anesthetized cats. Behavioral attacks similar to absence seizures could be provoked in behaving cats and monkeys by 3-Hz intralaminar thalamic stimulation. The response to this stimulation was called the arrest reaction. It is tempting to conclude that the manifestations of an absence seizure could be mimicked by electrical stimulation of the midthalamus, but only when the brain is in an appropriate state. Penfield introduced the term centrencephalic integrating system for the putative diffuse neural system projecting to both hemispheres, which was supposed to coordinate consciousness. This system was thought to be located in the brainstem and diencephalon. The centrencephalic system was held responsible for the generalized seizures with an initial loss of consciousness and a bilateral onset as seen in the EEG. Seizures were therefore called centrencephalic seizures and the underlying theory, the centrencephalic theory (Figure 1).

EVIDENCE OF A LEADING ROLE OF THE CORTEX: THE ROOTS OF A CORTICAL THEORY

Although the hypothesis of a central pacemaker for the generalized discharges received support, it also raised concerns as evidence was obtained for a leading role of the cortex. Already in 1952, Gibbs and Gibbs suggested that spike-wave discharges are generated in the cortex depending on diffuse cortical processes. Findings in patients also raised serious doubts about the validity of the centrencephalic theory. Bennett in 1953 showed in patients with petit mal seizures that injection of the convulsive drug pentylentetrazol in the carotid artery, supplying the cortex, produced generalized spike-wave activity. In contrast, such responses were absent when this drug was injected in the vertebral artery, which supplies the diencephalon and brainstem. Gloor was able to confirm these findings in pa-
patients and in cats. Unilateral intracarotid injection of pentylentetrazol in patients with generalized seizures elicited prolonged bilaterally synchronous generalized paroxysmal discharges, which clinically resembled the petit mal status. On the other hand, intravertebral administration attenuated the seizure discharges. These findings formed the basis for Gloor’s concept of generalized corticoreticular epilepsies.

One argument advanced by Penfield and Jasper in support of the centrencephalic theory was the impossibility of cortical lesions or cortical electrical stimulation to evoke a petit mal or grand mal attack. However, Bancaud discredited over the cortex through corticocortical pathways. Other proponents of the cortical theory on the basis of clinical observations were Lüders et al and Niedermeyer. According to these authors, primary generalized epilepsy is the expression of a cortical abnormality. The thalamus certainly participates but is only secondary in carrying out normal physiologic thalamocortical interactions. Generalized spike-wave bursts in primary generalized epilepsies are generated in the mesofrontal cortex, from which they rapidly spread over other cortical areas. This view was based on the detection of a focal origin of generalized seizures when recorded with implanted depth electrodes and the possibility of evoking them by stimulation of the same electrodes. Analyses of time shifts between EEG channels during typical absence spike-wave discharges seem to be in line with the cortical theory. The bilateral synchrony appears not to be perfect; it is apparent only at normal paper speed. With advanced signal processing techniques, interhemispheric latency differences of up to 20 milliseconds could be measured. In brief, Bancaud, Lüders et al, and Niedermeyer pleaded for a more extensive role of the cortex in the genesis of absence epilepsy: the cortical theory of absence epilepsy (Figure 1).

THE CORTICORETICULAR THEORY: THE FELINE PENICILLIN GENERALIZED EPILEPSY MODEL

Gloor proposed that a corticoreticular mechanism was involved in the generation of spike-wave discharges. He assigned, in his corticoreticular theory (Figure 1), essential roles in the genesis of discharges to both the cortex and the reticular system of thalamus and brainstem. The hypothesis was further refined with an animal model developed by Prince and Farrell. They showed that penicillin was able to induce generalized bilaterally synchronous spike-wave discharges in the cat. This “feline penicillin generalized epilepsy” model was considered a model for human primary absence epilepsy. Low-frequency stimulation of the midline thalamus of cats evoking spindles or recruiting responses appeared to evoke bilaterally generalized spike-wave discharges after application of penicillin. The question as to whether the epileptic discharges were the result of abnormal responses of the cortex or abnormal volleys from the thalamus was answered by an experiment in which diffuse cortical application of penicillin was also able to produce spike-wave discharges, whereas an injection of penicillin in the thalamus failed to do that. Gloor and colleagues stated that the crucial factor responsible for the spike-wave discharges was a diffuse increase in the excitability of the cortex. In this hyperexcitable epileptogenic state, cortical neurons respond to the afferent thalamocortical volleys by producing spike-wave discharges instead of spindles. The presence of both the thalamus and cortex proved to be essential for the typical spike-wave discharges to develop, while the bilateral synchrony of the spike-wave discharges appeared to depend on the corpus callosum. Phase-locked firing started a few cycles earlier in the cortex than in the thalamus. This suggests that the cortex first initiates the paroxysmal oscillation of the spike-wave burst and secondarily entrains the thalamus. Once the oscillation is set into motion, however, the thalamus and cortex appear to drive each other, as indicated by thalamic neurons firing either slightly earlier or later than their cortical counterparts. Currently, the corticoreticular theory seems still to be the most widely accepted of the absence theories, although the relative contributions of cortex and thalamus and the exact mechanisms are still matters of debate. It may, however, be questioned how valid this model is for human idiopathic generalized epilepsy. The main disadvantage of the feline penicillin model is that the role of the cortex may have been overemphasized, as the spike-wave discharges could mainly be a result of the pharmacologically induced increase in cortical excitability.

BACK TO THE THALAMIC PACEMAKER: THE INTRATHALAMIC NETWORK

Buzsáki in 1991 investigated the thalamocortical mechanisms of spontaneous spike-wave discharges (high-voltage spindles) occurring in a specific rat strain, Fischer 344 rats. Thalamic high-voltage spindles survived cortical ablation, whereas the cortical high-voltage spindles were abolished after thalamic lesions. More specifically, selective lesions of the reticular thalamic nucleus proved to suppress high-voltage spindles. Unit recordings in freely moving rats showed that cortical cells and thalamocortical relay cells fire in synchrony with the EEG spike, whereas reticular thalamic nucleus neurons fired during the slow-wave component. Local high-voltage spindle field potentials appeared to start a few cycles earlier in the thalamus than in the cortex, while rhythmic cell population firing in the thalamus built up gradually before the discharges became visible in the EEG. On the basis of these observations, Buzsáki proposed that a “thalamic clock,” which is the result of “emergent network properties,” is responsible for the discharges. The thalamic clock theory is shown in Figure 1. The reticular thalamic nucleus contains the pacemaker cells for the thalamic clock. Phasic bursting in a few reticular nucleus cells induces bursting in several thalamocortical relay cells, which in turn excites more reticular thalamic cells. Through the divergent projections between reticular thalamic and thalamocortical relay cells, more and more cells become recruited with each cycle of the oscillation, until the entire thalamic network is entrained in the rhythmic discharges. Hence, the rhythmic
epileptic discharges in the EEG are the result of an abnormal rhythmic oscillation in the intrathalamic network, which imposes its rhythm on the cortex. In this way, Buzsáki’s resurrected the centrencephalic concept.

Several findings in 2 other rat strains, both validated models for human absence epilepsy (the genetic absence epilepsy rats from Strasbourg [GAERS], reviewed by Danobe et al., and the Wistar Albino Glaxo/Rijswijk [WAG/Rij] rats, reviewed by Coenen and van Luijte-laar), appear to be in line with Buzsáki’s hypothesis. First, in GAERS, evidence was found for the pacemaker role of the reticular thalamic nucleus within the intrathalamic network. Selective lesions of the reticular thalamic nucleus suppressed spike-wave discharges. Moreover, in both WAG/Rij rats and GAERS, it was found that EEG spike-concurrent phase-locked cell firing in thalamocortical relay nuclei appeared to precede neocortical cell firing by a few milliseconds. This indicates that thalamocortical relay cells drive cortical cells, supporting the view that the thalamus acts as a generator of the cortical discharges.

**GENESIS OF SPIKE-WAVE DISCHARGES STUDIED IN THE WAG/RIJ MODEL**

To elucidate the neuronal network mechanisms that generate the spike-wave discharges and govern the widespread synchronization of the discharges, Meeren reviewed the role of the cortex in the genesis of discharges was tested. Large thalamic lesions, with destruction of the complete reticular thalamic nucleus and the specific thalamic relay nuclei, resulted in a complete disappearance of spike-wave discharges. Also, lesions that were restricted to the reticular thalamic nucleus resulted in spike-wave suppression. This shows that the thalamus in general, and the reticular thalamic nucleus in particular, is necessary for spike-wave discharges to occur. Second, Meeren investigated the role of the cortex in the generation of spike-wave discharges. Cortical spreading depression was used to transiently deactivate the entire cortex. The effects of the deactivation procedure were investigated by simultaneously recording the cortical and thalamic EEGs in WAG/Rij rats. At the height of spreading depression, when cortical inactivation is complete, spike-wave discharges were abolished in both cortex and thalamus. Spike-wave discharges reappeared after a long recovery period. This shows that a functionally intact cortex is a prerequisite for spike-wave generation. The intrathalamic circuitry alone is not sufficient for cortical and thalamic oscillations to occur.

Finally, the spatiotemporal properties of spike-wave discharges were investigated to elucidate the immediate widespread generalization of the discharges. Field potentials were simultaneously recorded from multiple cortical and thalamic sites. The corticocortical, intrathalamic, and corticothalamic interrelationships between these field potentials were quantified by means of the advanced signal analysis method of nonlinear association analysis. In this way, a direct measure of the strength of association, and thus of the degree of correlation between the events recorded at the different sites, was obtained, which gives an indication of the degree of functional coupling between the underlying neuronal populations. In addition, the method provides the time delay between signals. Together, these 2 parameters provide evidence on the driver-response relationships between the respective neuronal populations.

**THE CORTICAL FOCUS THEORY**

The outcomes of the nonlinear association analysis of the multiple spike-wave discharges showed a consistent cortical “focus” within the parietal region of the somatosensory cortex throughout the seizure and across seizures (Figure 2). The spike-wave discharges recorded at other cortical sites consistently lagged behind this fo-
providing a resonant circuitry. Subsequently, thalamus, which becomes entrained into the oscillation, thus transforms the spike into spike-wave activity. During the first 500 milliseconds, the cortical focus was consistently found to lead its thalamic counterpart. Thereafter, cortex and thalamus were found to alternately lead and lag in an unpredictable way. All of these results are incompatible with the common assumption that the thalamus acts as the primary driving source for the discharges. Earlier findings on the cellular thalamicortical relationships in rats showing that thalamic units seem to lead cortical units might be explained by the fact that the cortical recordings in these studies were obtained from sites relatively far away from the perioral local site. This may result in different corticothalamic time relationships. Instead, the results indicate that a cortical focus plays a leading role in the generation of generalized spike-wave discharges. First, this is the site where a spike of each new cycle is originally generated. The large-scale synchronization appears to be mediated by the fast propagation of seizure activity from this focal site through corticocortical networks. Second, it initiates the paroxysmal oscillation within the corticothalamic loops. Once the oscillation has been set in motion, however, cortex and thalamus form a unified oscillatory network in which both structures drive each other. The role of the thalamus probably lies in providing a resonant circuitry to amplify and sustain the discharges.

It is proposed that the generation of bilaterally generalized spike-wave discharges is only possible in an anatomically and functionally intact corticothalamic network, which is in a suitable state to propagate seizures. This state is characterized by light to moderate hyperpolarization of the intrinsically bursting cortical pyramidal cells and of the thalamocortical relay and the reticular thalamic cells, which makes them highly prone to produce high-frequency bursts of action potentials. The initial event is the generation of a normal or epileptic spike at the site of the cortical focus. Through the presence of a massive interconnectivity of excitatory cells, the cortical network is extremely susceptible for the generation of “runaway” excitation, if this network is not sufficiently controlled by inhibition, as is described for WAG/Rij rats. In such a runaway condition, the synchronous bursting of a few pyramidal cells may result in a rapid excitation of other excitatory cells, causing a rapid recruitment of neurons, accumulating into the generation of an epileptic spike. The initial leading spike always appears at first in a circumscribed area of the perioral region of the somatosensory cortex. The spike rapidly spreads over the cortex, thus giving the discharges their generalized appearance. This initial event sets a cascade in motion within the intact thalamocortical network, which transforms the spike into spike-wave activity. During the first few cycles the cortical focus drives the thalamus, which becomes entrained into the oscillation, thus providing a resonant circuitry. Subsequently, thalamus and cortex start to drive each other, hereby amplifying and sustaining the discharges. The rapid generalization of the spike-wave activity over the cortex is due to short-range intracortical fibers and to a subpopulation of cells that have long-range association fibers. These run under the cortex in the white matter, making extensive connections with other cortical areas. This allows for the fast widespread intrahemispheric distribution of activity and the interhemispheric transfer through the callosal fibers. From here the activity spreads again through the local network. Thus, the overall pattern of spread is the result of a combination of local and distant spread. Through its impairment in γ-aminobutyric acid–ergic inhibition, the intracortical networks of the WAG/Rij rat are highly susceptible to such spread. The perioral part of the somatosensory cortex may experience a more severe local impairment of γ-aminobutyric acid–ergic inhibition, turning it into a weak cortical focus or “hot spot,” with a low threshold for spike generation. This cortical focus is the prime mover of the discharges but, in the later interaction between cortex and thalamus, forms this “cortical focus” theory of generalized absence seizures (see Figure 1), a synthesis between the cortical and the corticoreticular theories.

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