

Absence Epilepsy from the Perspective of Neurophysiology

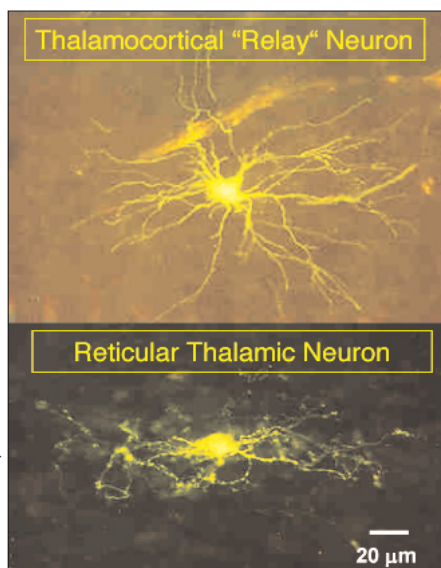
– Network Phenomenon and Ion Channel Disease –

Despite intensive research and clinical effort, the unequivocal diagnosis of absence epilepsy cannot be clearly established in all cases. Besides, the discrepancy between conclusions drawn from neurophysiological research and molecular genetics research on the one hand, and clinical findings on the other, is still very large. Basic research already offers a few interesting approaches that could exert an enduring effect on the future of patients with absence epilepsy as well as therapeutic options for future treatment of the disease. Of crucial importance here is the scientific finding that the thalamus – particularly its reticular portion – and parts of the somatosensory cortex play a very important role in the pathophysiology of absence epilepsy. However, a single isolated region in the brain can never explain the entire clinical symptoms and pathology of a disease. It should be mentioned that absence epilepsy essentially is a “network phenomenon”. In the healthy brain the thalamus acts as a pacemaker and contributes significantly to rhythmogenesis. Animal experiments on genetic rat models for absence epilepsy (GAERS; WAG-Rij) have shown that some of these pacemaker mechanisms which result from the interaction between ion flows of the neuronal cell membranes may be altered in terms of pathophysiology and eventually cause abnormal rhythms by way of the spike-wave discharges typically seen in absence epilepsy. Future efforts in therapy should focus on the development and application of specific substances that attack these pacemaker mechanisms. At the 19th meeting of the closed interdisciplinary research group “Berliner Kreis” (Berlin Circle) supported by Desitin Arzneimittel GmbH (Hamburg), held mid-January 2007 in Münster, the editorial team of NeuroNews.de had the opportunity to conduct an exclusive interview*) with Univ.-Prof. Dr. Hans-Christian Pape from the Institute of Physiology I, University of Münster, on the subject of Absence Epilepsy.



Source: University of Münster

Interview with Univ.-Prof. Dr. Hans-Christian Pape, Institute of Physiology I, University of Münster, Germany



Source: University of Münster

NeuroNews: Professor Pape, you have been invited to the 19th meeting of the “Berliner Kreis” (Berlin Circle) this year and asked to speak about the main topic of the event, which is Absence Epilepsy. What importance do you assign to the fact that this subject is being addressed in detail at this meeting?

Prof. Pape: I believe it is extremely important and also desirable that the field of basic re-

search is entering the domain of clinical perspectives. Conversely, I also think it’s very significant that clinicians are concerned with the mechanisms that have been disclosed by basic research and these mechanisms are becoming part of the clinician’s approach. This will contribute significantly to enhancing the dialogue between the two groups. Particularly with regard to absence epilepsy there still is, in my opinion, a large discrepancy between the conclusions drawn from animal experiments and genetic research on the one

Fig. 1. Relay neuron and reticular neuron of the thalamus

hand, and clinical findings on the other. This is no evaluation. It is only meant to draw attention to the gap that actually exists and has to be bridged as soon as possible. For instance, basic research already offers interesting approaches to the development of new drugs that are expected to be able to suppress epileptic attacks in a more specific way and without the known side effects of the substances currently in use.

NeuroNews: *What is the prevalence of absences in Germany and in what age groups is this condition primarily diagnosed?*

Prof. Pape: This form of generalized epilepsy occurs most commonly in childhood and adolescence. The age group of 6- to 7-year-old children apparently is most frequently affected by the disease. In Germany the prevalence of absences is about 0.5 to 0.8%

NeuroNews: *What regions of the brain play an important role in the pathophysiology of absence epilepsy?*

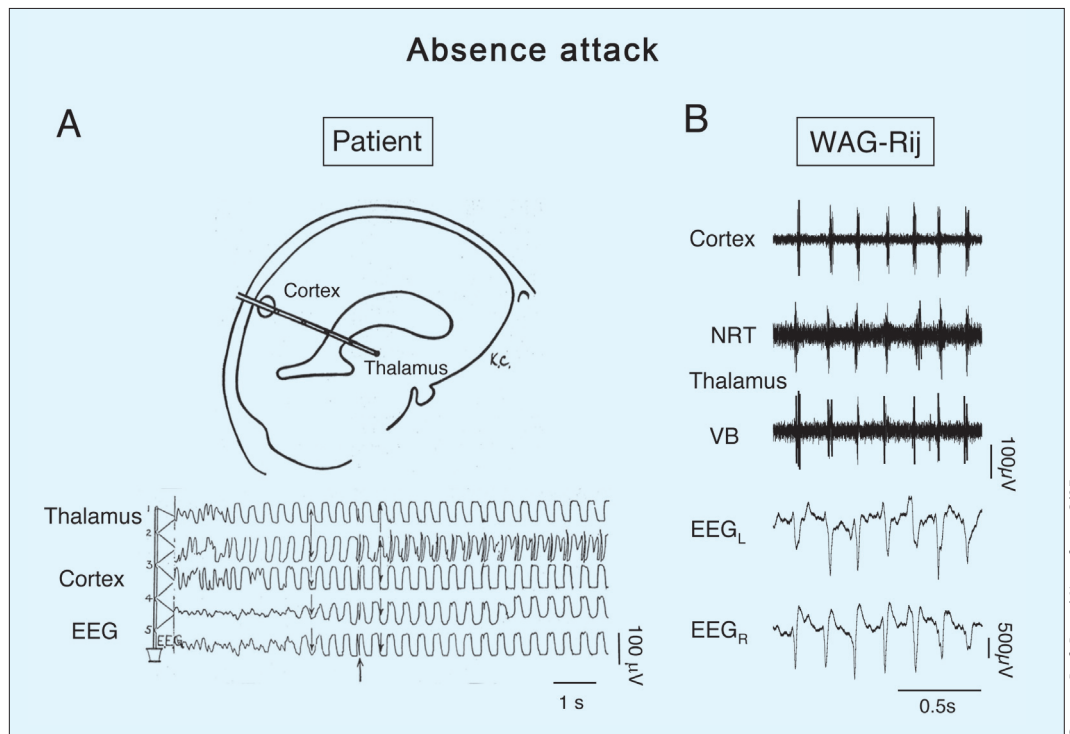
Prof. Pape: Primarily the thalamus – and also specific regions in the cortex – are involved in the pathophysiology of absence epilepsy. However, we should bear in mind the fact that absence epilepsy is a network phenomenon. A single isolated region in the brain can never explain the entire clinical symptoms and pathology of absence epilepsy. If we wish to identify so-called hot spots, we should first

think of the reticular portion of the thalamus which is an important pacemaker, and regions of the somatosensory portion of the cortex. Both “hot spots” have been determined by measurements of different sensitivities to benzodiazepine. This association may also help to explain typical symptoms of absence epilepsy such as orofacial disturbances, which are remanifested in movements of facial muscles.

NeuroNews: *By doing intensive research you have been able to show that the neuronal activities of the thalamus are changed in patients with absence epilepsy. Could you elaborate on this association?*

Prof. Pape: As a pacemaker the thalamus contributes significantly to the rhythmogenesis of neurons and the brain. Like the pacemaker activity of the heart, this pacemaker activity is a re-

sult of the interaction of ion flows in the cell membrane. Ions flow through ion channels between the cell center and its periphery. Their periodic interaction explains this rhythmic activity. Pathophysiological changes in these pacemaker mechanisms and their significance in absence epilepsy were identified in experimental studies. Two of these pacemaker mechanisms are relevant here. On the one hand it is a mechanism that leads to perverted “burst discharges” through a voltage-dependent calcium channel. These burst discharges are the reason for the salvos of discharges or the spike-wave discharges observed by clinicians. On the other hand it is a so-called pacemaker flow or H-flow, whose control is altered. The control potential of the H-flow is reduced. This results in prolonged rhythmic discharges and changes in the normal rhythms in favour of spike-wave discharges.

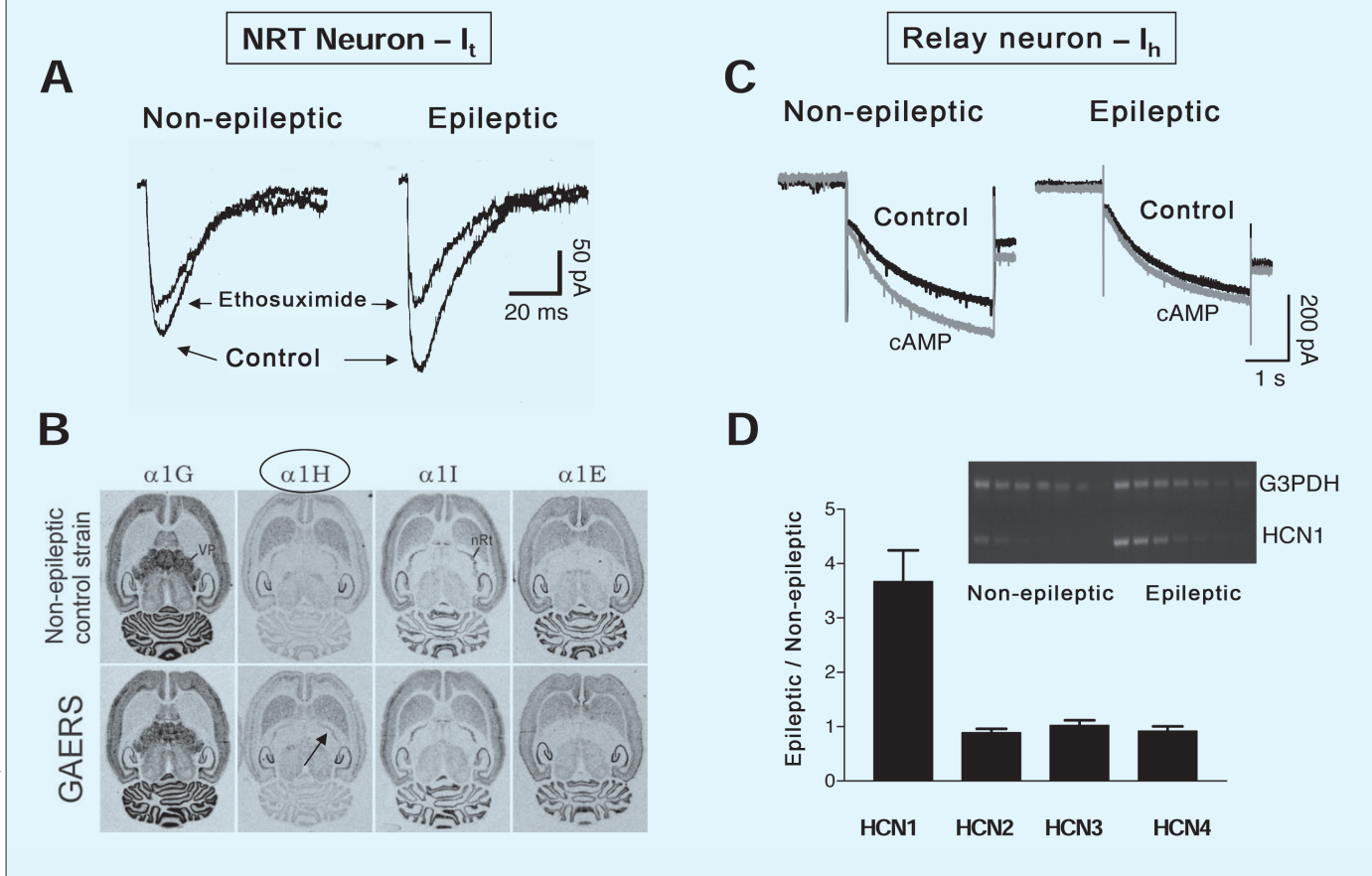


Neurophysiological correlates of an attack of absence epilepsy

(A) Registrations of surface and depth EEG in the cortex and the thalamus during an absence attack in a child (based on Williams, 1953). (B) Bilateral registrations of the EEG and simultaneous extracellular recordings in the somatosensory cortex. Nucleus reticularis thalami (NRT) and ventrobasal thalamic complex (VB) in a genetic rat model for absence epilepsy (GAERS). The epileptic attack is demonstrated on the EEG as spike-wave discharges (SWD), which are associated with synchronous discharges in extensive regions of the thalamocortical system.

Source: Prof. Pape / Neuroforum 2/05

Absence epilepsy – ion channel dysfunctions



Source: Prof. Pape / Neuroforum 2/05

Absence epilepsy and ion channel dysfunctions in neurons of the reticular thalamus (NRT) (left column) and relay neurons of the thalamus (right column)

Visualization of I_t (voltage clamp experiment) in acutely isolated neurons of the NRT from a genetic rat model for absence epilepsy (GAERS) and non-epileptic control rats. Note the increased amplitude of I_h in epilepsy and the reduced effect of the anticonvulsant ethosuximide (based on Tsakiridou et al., 1995). In situ hybridization shows a significant and selective increase in the expression of the 1H (CaV3.2) subunit of the T-type Ca^{2+} channel in NRT in GAERS (based on Talley et al., 2000) Visualization of I_h (voltage clamp experiment) in relay neurons of CGLd in a sectional sample from a genetic rat model for absence epilepsy (WAG/Rij) and non-epileptic control rats. Note the reduced effect of cAMP in epilepsy. Differences in the mRNA expression pattern of subunits of I_h , HCN1-4, in epileptic and non-epileptic CGLd, demonstrated with the aid of semiquantitative RT-PCR (the additional illustration shows the example of a corresponding PCR profile). Note the significant and selective increase in the expression of the HCN1 subunit in epilepsy.

NeuroNews: In your lecture you spoke about the fact that absence epilepsy is an "ion channel disease". In this context – what is the role of reticular thalamic neurons in respect of spike-wave discharges and how are these discharge patterns generated?

Prof. Pape: As mentioned earlier, spike-wave discharges are a network phenomenon in which networks interconnected by synapses lead to a temporally synchronized group of discharges. Within these networks, individual cells that are coupled with each other and act as oscillators play a very important role.

The neurons of the reticular thalamus occupy a strategically important position between the thalamus and the cortex, control the signal flow between these two regions in the brain, and are considered to be the initiators of oscillations. These oscillators act through ion channels in the cell membrane, which are altered by genetic factors such as those associated with amino acid sequences. The ion channels thus mutated cause the oscillations to turn pathological in terms of spike-wave discharges. Thus, absence epilepsy may also be regarded as an ion channel disease. Normal physiological functioning is no longer possible.

NeuroNews: What genetic factors play a role in the emergence of absence epilepsy?

Prof. Pape: Here one must distinguish between factors that have been found in so-called linkage studies and those identified by gene analysis in humans. In these linkage studies, on the one hand a voltage-dependent calcium canal, the so-called PQ- or the $\alpha 1A$ -type plays a decisive role. One investigation of several generations of an epileptic family disclosed a mutation that causes these specific calcium channels in the neurons of the brain to be expressed in a different way, or disclosed the pres-

ence of these calcium channels, and showed that they contribute to perversion of the activity pattern. The latter is responsible for the typical spike-wave discharges seen in absence epilepsy. On the other hand, a few years ago an allelic polymorphism of a γ -2 subunit of the GABA_A receptor was identified. One of its effects, for instance, is that sensitivity to benzodiazepine is reduced. This also contributes to perverted discharge patterns in the relevant circuits of absence epilepsy.

NeuroNews: *To what extent could these research results contribute to improving the treatment of absence epilepsy?*

Prof. Pape: First of all, let me mention a few important facts about diagnosis. Absence epilepsy cannot be clearly diagnosed in all cases. Nevertheless, in the future it should be possible to identify this disease with much greater certainty by means of gene analysis or so-called molecular medicine. In the field of therapy it would be meaningful to apply – in a targeted fashion – substances that attack the above mentioned pacemaker mechanisms. Some approaches here would be, for instance, subunits of calcium channels which are known to be altered in absence epilepsy. We have yet to find antagonists that apply to, and act on, all of the subunits for any of the demonstrated mechanisms. However, based on knowledge gained from basic research it will be possible to broach a new path in pharmacological research and develop substances that attack the above mentioned ion channel subunits.

NeuroNews: *Is this only wishful thinking – considering the fact that any treatment with antagonists that attack specific*

subunits of calcium ion channels could also impair the rest of the human organism?

Prof. Pape: The subunits of the ion channels are marked by their specific regional distribution. Let us assume that an ion channel consists of four subunits. These are not uniformly distributed in the organism. Rather, they are distributed in various regions of the brain and in different cell types. At these sites they have a very specific distribution pattern of expression. The genome is similar. However, expression, which occurs through targeted copying of individual genes, is a cell-typical phenomenon. Therefore, one might be able to interact in a cell-typical manner through subunit-specific manipulation or at least region-specific manipulation. That, I think, is the pathway to be adopted by pharmaceutical medicine or the pharmaceutical industry in order to make advancements in the treatment of absence epilepsy – apart from the genetic options. We have data from neurophysiological basic research on this subject and can provide this knowledge at any time. Implementation of the knowledge is the domain of biochemists or chemists.

NeuroNews: *Do you anticipate new findings from your field of basic research that will influence the future of patients with absences in an enduring manner?*

Prof. Pape: There are regions in the thalamus, so-called intralaminar thalamic nuclei, which are very diffusely connected in the cortex and are able to synchronize large areas. Besides, the data of patients investigated by a Mexican work group have shown that electrical stimulation of these thalamic neurons can very effectively interact with the activity of epileptic attacks.

A group of scientists from Zurich also concluded that surgical resection of the intralaminar nuclei in the thalamus may favourably influence a number of psychiatric or neurological symptoms. However, we still lack in actual

»It should be mentioned that absence epilepsy essentially is a network phenomenon.«

basic science data on this subject. I think research must continue from this point to identify the above mentioned mechanisms. I personally believe that such research on the subject of the intralaminar thalamus is a very promising field and hope the results will also positively influence the future of patients with absence epilepsy.

NeuroNews: *Professor Pape, thank you very much for this interview.*

**) The interview was conducted in Münster on 20th January 2007 by Dr. Susanne Schweizer on behalf of NeuroNews.de.*

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