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Anti-epileptogenesis research : the clinical relevance

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On behalf of the Flemish Circle of Epilepsy

Abstract

In recent years, different research lines have examined the epileptogenic process in order to understand the different stages in this process, and with the hope that early recognition and intervention could prevent chronic epilepsy in patients with epileptic seizures. In animals, acquired epilepsy is studied most commonly with kindling models, status epilepticus models and traumatic brain injury models. Molecular genetic studies substantially help to understand age-specific channel and receptor abnormalities. Major progress has been made in recent years and we are now waiting for the first large scale multi-center clinical trials that test the possible anti-epileptogenic properties of anti-epileptic drugs or other compounds in well defined patient groups. In clinical practice, a structured diagnostic work-up in all patients with recurrent seizures is a first and necessary step in the recognition of patients at risk for developing chronic and refractory epilepsy.

Key words : Epilepsy ; epileptogenesis ; anti-epileptic drugs ; animal models ; neuroprotection ; seizures.

Introduction

Why do we treat patients with epileptic seizures ? The textbook answer is obvious and well known : to prevent recurrent seizures. Prevention of seizures will minimize secondary morbidity from epilepsy-related injuries. Recent studies have also shown that sudden unexplained death in epilepsy (SUDEP) occurs more frequently in under-treated epileptic patients (Nilsson *et al.* 2001). Further, control of seizures will minimize the still underestimated negative social impact of epilepsy. In a way, for many patients, control of seizures is a prerequisite for work, driving and normal social life.

Although these goals can be achieved in the majority of patients, neurologists realize that standard treatment with anti-epileptic drugs may not significantly influence the epileptic process, or *epileptogenesis*, itself (Schachter S. C., 2002). In clinical practice, one can *retrospectively* distinguish different patient groups with epilepsy. There are patients who become seizure free with standard anti-epileptic drugs. Some of these patients remain seizure free after withdrawal of medication. In other patients, seizure control can not be achieved despite different anti-epileptic drugs. The important question in clinical practice therefore is whether the outcome can be predicted already at the start of the epilepsy.

In patients with lesional epilepsy, it appears that only complete removal of epileptic tissue can stop the epileptic process. In other patients, we do not have consistent indicators that predict if treatment will be successful, or if the patient will become refractory to medication and show signs of cognitive decline (Kwan and Brodie, 2000). Also not well understood is the spontaneous cessation of epileptic seizures in some childhood epilepsy syndromes. Progress in the genetic background in some of these syndromes indicates that there might be an age-related expression of ion channel abnormalities in these syndromes, explaining why some syndromes start and stop at certain ages (Kullman, 2002 ; Szepetowski *et al.*, 1998). In these syndromes, such as the benign occipital and rolandic epilepsies, it is as if epileptogenesis is an age-dependent phenomenon.

One of the main issues nowadays in epilepsy research is to try and fully understand epileptogenesis, to identify the patients at risk for chronic epilepsy and to find new treatment options to prevent chronic epilepsy in these patients (Cole A. J., 2000).

In recent years, many data have become available that help to explain the natural epileptic process, both in rodents and humans. It became clear that different stages in the epileptic process can be distinguished. The disease “chronic epilepsy” therefore is the result of different contributing factors with different weighting factors : genetic predisposition, brain maturation, underlying brain abnormalities, seizures-related damage, (un)known neuromodulators and time.

In this paper, we will review the experimental evidence illustrating the existence of different steps in the epileptogenic process. Especially, we want to identify possible opportunities in clinical practice to intervene by preventing, modifying or stopping

this epileptogenic process. In patients diagnosed with epilepsy, early intervention in the epileptogenic process could prevent the development of intractable epilepsy. In this way, in the future, one hopes to move from *symptomatic seizure treatment* to *preventive epilepsy treatment.*

Epileptogenesis

First, it is important to identify and characterize the different patient groups that do develop chronic epilepsy. Theoretically, this allows to find common characteristics and subsequently deduct risk parameters. Also, these insights have contributed to the development of animal models that mimic as much as possible the human disease, although there are many potential pitfalls in the animal-human comparison. Any insult to the brain can trigger an epileptic seizure, but only a minority of the patients with single seizures will develop chronic epilepsy (Forsgren L, 1990). Several studies have addressed this issue. In a recent review, the disease entities with the highest risk for developing epilepsy were described (Herman, 2002). Five diseases are associated with a very high risk factor (at least 20 times more chance than a control patient to develop chronic epilepsy) : brain tumors (40x), mental retardation/cerebral palsy (27x), subarachnoid hemorrhage (34x), hemorrhagic CVA (26x), and severe traumatic brain injury (29x). As already known in the pediatric neurology world, but still overestimated in the adult epilepsy world, only a minority of the children with febrile seizures will develop epilepsy (Annegers J. F. *et al.*, 1987).

However, it should be remembered that these symptomatic epilepsies account only for maximum 30%-50% of all the patients with epilepsy (Hauser W. A. *et al.*, 1996). This obviously limits somehow the relevance of the current experimental data on epileptogenesis if no other research strategies would be developed in the future. In many patients with epilepsy, a causative factor is not found ('idiopathic epilepsies'). Without any doubt, molecular genetics will continue to give more insight in the pathogenesis of both idiopathic and symptomatic epilepsy. However, it will not suffice to find causative mutations in ion channel genes (such as sodium channels, potassium channels or GABA receptors) but one will need to study the spatial and temporal distribution of the gene product throughout the brain and during lifetime. Indeed, transgenic mice models will be needed to explore these questions.

Is there a common brain disturbance in these epilepsy-prone diseases ? Actually, research has not provided definite answers. In general, one could hypothesize that lesion-induced impaired blood supply to critical brain regions is involved, perhaps together with a damaged blood brain barrier (Vaughan C. J. and Delanty N., 2002). This hypothesis would explain the relationship between the degree of traumatic brain injury and the subsequent frequency of epilepsy. Interesting recent data on the role of genetically-driven acute immunological markers, such as the interleukins, in epilepsy are intriguing and certainly deserve more attention (Peltola *et al.*, 2002 ; Kanemoto *et al.*, 2000). It is clear that there is a lack of neurobiological data that characterize the cellular and receptor changes at the beginning of the epileptogenic process and at the time of a seizure.

Animals models to explain the epileptogenic process

There is not an ideal animal model to explain all the issues involved in the epileptogenic process (Losher, 1997). As pointed out in detail in a recent overview, there is a risk of over-interpretation of animal models data (White, 2002). A thorough knowledge of the strengths and weaknesses of the current animal models is necessary to be able to understand the potential clinical correlates. As mentioned before, only the most frequent acquired epilepsies have been studied in detail with the use of animal models. In all these models, an initiating insult is used to trigger the epileptogenic process with a typical silent, latent period between the triggering event and the occurrence of epileptic seizures. Already at this point it should be stressed that this 'initiating insult' is not producing epilepsy in all animals, comparable with what is seen in human disease. Of course, the risk to develop epilepsy depends on the strength of the initial insult, but also on the timing of the insult. For instance it is known that a newborn brain is less vulnerable to develop epilepsy after an acute brain insult (Jensen and Baram, 2000 ; Lado *et al.*, 2000, Liu *et al.* 1996). Another point is the latency period : this period is very variable in many models, so that an artificial endpoint set by the experiment may bias the results.

The rodent models most frequently used to study acquired epilepsy are kindling models, status epilepticus models and traumatic brain injury models. In *kindling*, rats exposed to repetitive subconvulsive electrical simulation develop after some time clinical seizures with minimal stimulation, indicating that the kindling started the epileptogenic process (Losher 1997, McNamara, 1995). This model has several disadvantages (no spontaneous seizures, no real latent period), but has one advantage : the pathological changes that are seen over time are very similar to the ones seen in hippocampal sclerosis, at least when these brain structures are stimulated. Any experimental manipulation in this model can be verified pathologically. In the *status epilepticus model*, another common clinical situation has been tried to replicate. It is known that a long lasting seizure can be an initial event, after which patients develop chronic epilepsy (Hesdorffer *et al.*,

1998). However, one could also argue that the first prolonged seizure or status epilepticus is the first symptom of an already existing epileptic process, instead of labeling the status as the primary event. This idea of a status epilepticus being a 'second hit' is probably more relevant than initially believed (Walker *et al.* 2002). For instance, in patients with a cortical malformation, a second hit, such as a head trauma, a long lasting febrile seizure or a status epilepticus is sometimes 'needed' to start the epilepsy. This may explain the rather high number of asymptomatic patients with cortical malformations. Also, the second hit model may help to explain the variable age of onset of the epilepsy in patients with cortical malformations (Lagae, 2000). In the rodent model, different agents are used to provoke status epilepticus. In most models the limbic structures are stimulated electrically or chemically, therefore probably mimicking only one 'epileptic pathway'. In this model, a latent period can be observed and the seizures afterwards are spontaneous seizures. Here also, pathological changes are concordant with the clinical evolution of the animals. In some status epilepticus models, it has been shown that the timing of the status epilepticus is the crucial factor to predict the development of epilepsy (Sankar *et al.*, 2000). This last factor should be taken in consideration when studying the potential anti-epileptogenic effect of drugs. Previous studies have shown already that there might be a time window for prevention of epilepsy : if the status can be stopped within that time window, chronic epilepsy will not develop (Bolanos *et al.*, 1998 ; Klitgaard *et al.*, 2001, Prasad et 2002). Some drugs have claimed this neuroprotective label, although here also, more systematic studies are needed. Perhaps all drugs that can stop a status epilepticus in time could be neuroprotective. The *traumatic brain injury models* try to mimic the clinical situation after severe head trauma and also after stroke. In these models, the key finding is an increase in hyperexcitability, as illustrated for instance by increased NMDA receptor conductance or altered glutamate transport (Bush *et al.*, 1999). It is somewhat surprising, looking to the available literature, that especially in this model, not more fundamental neurobiological changes have been studied. The last model that deserves more attention, especially in view of the important timing effect of the initial event, is the *hyper-thermic seizures model*. In this model, seizures are induced with manipulation of body temperature, mimicking febrile seizures. The clinically relevant question here is not only if there is a relationship between early prolonged febrile seizures and later hippocampal sclerosis, but also why only a minority of the children that have prolonged febrile seizures ultimately develop epilepsy. Is timing the most crucial factor, the length of the seizure, the initial (neuroprotective) management, the degree of blood brain barrier disruption, a genetic predisposition or an unidentified second hit in later life (Chen *et al.*, 2001) ?

Steps in epileptogenesis

Perhaps one of the most relevant findings is that animal studies have identified different sequential steps in the epileptogenic process, that could each become a target for therapeutic action (Pitkanen, 2002). At a first level, 'modification' of the acute insult could become an early treatment option. As pointed out, a prolonged seizure or a status epilepticus, especially at a vulnerable age, can trigger the start of the epileptogenic process. Even though no formal clinical studies are available that address this issue (Temkin 2001), it is more than reasonable to treat a status epilepticus adequately, underlying the importance of a standardized protocol in every neurology service. Once the acute event has terminated, a classical latency period starts in many of the experimental models of acquired epilepsy. Another therapeutic option therefore could be to start anti-epileptic drug treatment in order to prevent the development of chronic epilepsy. This is the story of 'prophylactic' AED treatment after stroke, status epilepticus or even brain surgery. There are still not enough clinical data to support this treatment option (Temkin 2001). Standard treatment with anti-epileptic drugs will prevent a second seizure in many patients, especially in the early phase, but this is no guarantee that it will prevent epilepsy at a later age. In the latency period, other interventions will undoubtedly become new strategies in the near future. For instance, gene therapy introducing proteins that block apoptosis (McLaughlin *et al.* 2000), and 'vaccination' induced antibodies against the excitatory glutamate receptor (During *et al.*, 2000) are promising options.

Once the epilepsy starts, disease modification could help to prevent drug refractory epilepsy or to prevent the secondary changes seen in epilepsy, most importantly cognitive decline. Here, another fundamental question in this research field arises : once the epilepsy is established, is there a continuing epileptic process, or has the remodeling and rewiring in the brain come to an end ? In the former and more realistic case, it would indicate that there still remains an opportunity to modify the disease ; in the latter case, we would be left with classical symptomatic treatment of seizures. There is enough evidence to support the first hypothesis, at least in a sub-population of the patients with acquired epilepsy (Ptikanen and Sutula 2002). This is the field where fundamental research and clinical epileptology should interact. If clinicians would be able, based on clinical, neuro-imaging, EEG or other data, to identify epileptic patients at risk for the development of refractory epilepsy, then more specific therapeutic strategies could be applied. A

classical example is the finding of mesial temporal sclerosis in a patient with temporal lobe epilepsy. Do we support the logical strategy to remove the damaged hippocampal region, even though the epilepsy is still under control with a first line anti-epileptic drug ? Or do we wait until the epilepsy becomes refractory and the patient shows subtle cognitive decline before epilepsy surgery is considered ? At this time, many epilepsy centers still go for the latter option, but this might not be optimal strategy, in view of the available data on epileptogenesis.

Related to this issue is the question whether the variety of newer anti-epileptic drugs is somehow modifying the epileptogenic process. The caveat here again is a too fast extrapolation of current experimental data. On the other hand, there are enough clinical examples in recent years that support the notion that some anti-epileptic drugs do change the natural history in some epilepsy syndromes. Take the example of infantile spasms in the setting of a West syndrome. The introduction of vigabatrin as a first line treatment for this catastrophic epilepsy syndrome has changed the epileptic and cognitive outcome substantially. Also, the natural course of children with other refractory epilepsies, such as severe myoclonic epilepsy of infancy (SMEI) or Lennox Gastaut syndrome, has changed in recent years, probably due to the earlier use of the newer anti-epileptic drugs. In SMEI for instance, the best treatment to lower the number of status epilepticus periods seems to be valproic acid combined with topiramate and benzodiazepines. The effect on the cognitive level is less clear. Of course, these clinical examples are no formal proof that these new drug combinations are disease modifying. The difference between pure anti-epileptic effects and possible disease modifying effects is very hard to distinguish.

Conclusions

Although everybody will agree on the importance of in depth studies in animal epilepsy models, their clinical relevance is rather discouraging until now. The first and most important reason is the fact that the neurobiological changes induced by an acute seizure are not yet understood. Here, molecular genetics will help in the future. Secondly, the current animal research only model some forms of acquired epilepsy, and experimental results should not be over-interpreted. Although there are indeed promising results with the newer anti-epileptic drugs in the field of anti-epileptogenesis, more large scale clinical studies are needed, and not only with AEDs but also with other potential disease modifying substances. The identification of different steps in anti-epileptogenesis allows us now to think in a much more structured way about epileptogenesis. From this, the following consequences for clinical practice could be considered.

In every patient presenting with epilepsy, a thorough and standardized diagnostic work-up should be performed. An unresolved but crucial issue for clinical practice, is whether this diagnostic process should start after a first seizure or after the establishment of the diagnosis epilepsy. The aim is to understand as much as possible the underlying abnormalities in patients with seizures. Indeed, this is a plea for a correct diagnosis. The diagnostic work-up includes at least full personal and family history, clinical examination, including ophtalmoscopy and MRI. A standardized file system to follow the patient is recommended. In modern molecular genetics times, DNA sampling should also be considered. This diagnostic round will certainly allow earlier identification of some patients at risk for difficult to treat or refractory epilepsy. The finding of mesial temporal sclerosis for instance should start a therapeutic process that already at the beginning considers epilepsy surgery as a treatment option. Two or more prolonged and especially lateralized febrile seizures in a young child, should be considered as a diagnostic challenge. A patient that presents with very frequent seizures or with a status epilepticus should also be considered as a potential candidate for refractory epilepsy. Likewise, if standardized treatment fails in a new patient, this should be considered as a potential risk for later refractory epilepsy. Perhaps, we should also discuss this earlier with these patients at risk. On the other hand, identification of patients who are at risk to develop chronic and sometimes refractory epilepsy is merely a starting point. Multi-center trials to test anti-epileptogenic properties of AEDs or other substances in well-defined patient groups will be a necessary next step. Unfortunately, despite overwhelming research data, we are still not 'beyond empiricism' in the treatment of epilepsy (Brodie and Leach 2003).

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