Animal models to study aetiopathology of epilepsy: what are the features to model?*

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ABSTRACT – In order to understand the physiopathology of epilepsies and develop antiepileptic drugs, animal models have been developed. These models appear to be valuable predictors of treatment efficacy; however, several of the currently used models remain questionable and probably inappropriate for the search for new treatments, in particular for epilepsies that cannot be treated by current antiepileptic drugs. In the present review, we report the results of a recent survey conducted by neurologists in charge of an epilepsy programme based at different hospitals in France. The 36 experts were questioned, *via* the internet, on the most critical features of four prototypic forms of epilepsy (idiopathic generalised epilepsies with convulsive seizures, absence epilepsy, focal epilepsy associated with dysplasia, and focal epilepsy associated with hippocampal sclerosis) that should be taken into account with regards to the relevance of animal models of epilepsy. Their answers suggest that most current models for focal epilepsies associated with either dysplasia or hippocampal sclerosis do not address the most relevant features. The models currently used in mice and rats are discussed in light of the data obtained in our survey.

Key words: animal model, absence epilepsy, temporal lobe epilepsy, dysplasia, preclinical research

After several years of research on the mechanisms underlying epilepsies and addressing the possibility of controlling seizures with better designed compounds, we have so far failed to provide innovative targets. This is particularly true for focal epilepsies that cannot be treated by current antiepileptic drugs (AEDs). One of the reasons appears to be a lack of relevant animal models corresponding to these forms of

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epilepsy which are particularly diverse, not only with regards to aetiology (malformative, vascular, post-traumatic, infectious, genetic) but also localisation (temporal, frontal, occipital, *etc.*). Animal models currently used exhibit features that are often very different from clinical conditions. Indeed, although it is quite understandable that a biological model is a simplified representation of a disease (Loscher, 1997), there are essential electroclinical and histological features that need to be modelled in order to provide data that can be transposed to the clinic. Several sophisticated animal models have been developed during the last 10 years either by classic (*i.e.* lesions, stimulations, genetic selection) or more modern methods (*i.e.* transgenesis, transfection, RNA interference) which display several EEG, behavioural or histopathological features reminiscent of a given form of epilepsy. Several of these models display a complex variety of features and the question remains as to which models should be selected that are the most relevant for the clinical situation. Indeed, too much complexity or simplicity in a model might lead to the development of drugs that are used to treat a disease that does not even exist in human patients. With the development of sophisticated genomic tools to generate new animal models with chronic occurrence of seizures, there is an urgent need to reconsider what are the most critical features for a given form of epilepsy to provide transposable data. In this review, we report our initial data on a recent survey, performed by French neurologists with a strong expertise in the treatment of epilepsies, in order to consider which features are essential to model four different prototypic forms of epilepsy: idiopathic epilepsy with generalised convulsive seizures, absence epilepsy, and focal epilepsies either associated with focal cortical dysplasia or hippocampal sclerosis, these two latter forms being particularly frequent in epileptic patients.

Methodology of the internet survey

In order to better determine the critical features of a given form of epilepsy that should be taken into account with regards to the relevance of an animal model, we conducted an internet survey, (Google documents) sent to 58 neurologists working in epilepsy centres in 21 hospitals in France. They were asked to answer six different questions anonymously on the modelling strategy (type of preparation and animal species) and state which features/symptoms they would consider relevant in order to model the four different prototypic forms of epilepsies indicated above. They were asked to choose three possibilities among 10 to 15 possible answers (https://docs.google.com/spreadsheet/viewform?formkey=dFByc3ZfMGRRdFpoRUxpVWJTWDdSY1E6MQ).
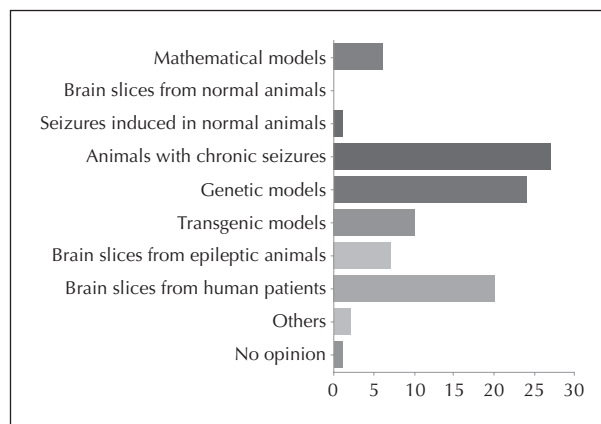

Figure 1. Type of models. The number of features selected (maximum of three/individual) by 36 clinical experts in epileptology to answer the question: "*In your opinion, which type of models would provide the most reliable information about epilepsy for clinicians?*"

This survey was conducted over a period of a month (October through November, 2011) and was completed by 36 clinicians. The results of this study are presented below in each section and the models that are currently used for these corresponding forms of epilepsy are discussed in the light of the clinician's requirements.

The need for chronic animal models

When asked which type of models should provide the most reliable information on the physiopathology of epilepsies, animals with chronic seizures (75%), genetic models (67%), and slices from human brain tissues (56%) emerged as the most relevant, according to our panel of clinicians (*figure 1*). On the contrary, preparations using normal animals either alive (*e.g.* pentylenetetrazol, electroshock) or *via ex vivo* brain slices were rarely considered (0 and 3%, respectively). Transgenic animals (28%) and mathematical models (17%) raised some interest and their low scores may be explained by their recent development. When asked about the animal species that should be used to obtain the most reliable data for the clinic, the largest score corresponded to monkeys (67%) (*figure 2*). However, rats (61%) were also largely considered and, to a lesser degree, mice (39%) and pigs (25%), although no models have been developed so far for the latter.

Although the results of these first two questions were somewhat predictable, they confirmed the clinical relevance of "*epileptic animals*", *i.e.* animals with spontaneous and chronic recurrent seizures, resulting from genetic selections or manipulations, or from an initial trauma. It is important to note that data obtained from slices of resective tissue of epileptic patients are
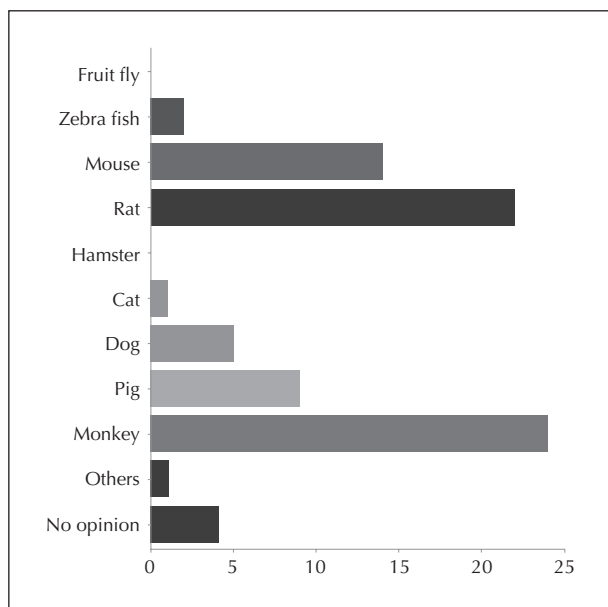
Figure 2. Animal species. The number of features selected (maximum of three/individual) by 36 clinical experts in epileptology to answer the question: "*In your opinion, which animal species would provide the most reliable information about epilepsy for clinicians?*"
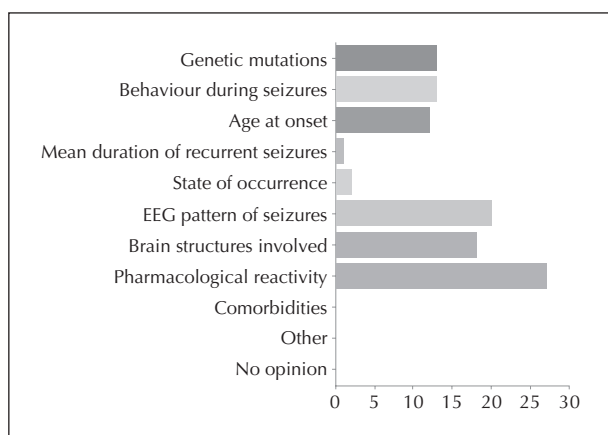

Figure 3. Idiopathic epilepsy with generalised convulsive seizures. The number of features selected (maximum of three/individual) by 36 clinical experts in epileptology to answer the question: "*In your opinion, what are the most important clinical features that should be present in an animal model, considered by clinicians to be relevant to generalised convulsive epilepsy?*"

considered to have a great relevance by clinicians. Despite the somewhat artificial conditions, the fact that they provide data for human tissue certainly makes such preparations more transferable to the clinic. It is also likely that recent publications from French groups using this approach (Huberfeld *et al.*, 2011; Cohen, 2002) have "sensitized" the members of our panel and these data will be interesting to compare when the

same survey is performed by experts in other countries. In contrast, almost no relevance was given by the clinicians to data collected in the "one shot" preparations such as *ex vivo* slices from normal animals or models where acute seizures were induced. Although confirmation is required using a larger population of neurologists, these results clearly indicate the need for animal models that are more closely related to clinical situations and suggest that clinicians may become less and less confident in AED treatment for which preclinical data are essentially obtained in such models. However, this may depend on the type of epilepsy concerned; in the present study, it was necessary to further examine the opinion of clinicians for four prototypic forms of epilepsy.

Modelling idiopathic generalised epilepsies with convulsive seizures

For models of idiopathic generalised epilepsies (IGEs) with convulsive seizures, reactivity to AEDs clearly emerged as the most important feature by clinical epileptologists, with 75% responding positively (*figure 3*). The EEG patterns of the seizures and the similarities of the brain structures involved were also important features (56 and 50%, respectively). Surprisingly, only 36% of the clinicians considered that genetic mutations should be taken into account and 33% considered the age at onset and the behaviour during seizures should be taken into account. IGEs with convulsive seizures are classically modelled by tonic-clonic seizures induced by electroshock or pentylenetetrazol injection. Indeed, both models have a pharmacological reactivity that is relatively predictive for generalised convulsive seizures and they have proven to be useful in drug development. However, to what extent these models increase our understanding on the physiopathology of these forms of epilepsy remains questionable. It is also very likely that they are not predictive for other forms of epilepsy, such as focal epilepsies.

A few genetic models with spontaneous generalised convulsive seizures have been described (Noebels, 1999). Most of them are monogenic but often display a complex phenotype, in addition to convulsive seizures. The sporadic occurrence of the spontaneous seizures, the difficulties in maintaining the lineage, and the lack of both EEG and pharmacological information on these models make them difficult to use during the preclinical development of a candidate AED. Rodent strains which demonstrate seizures triggered by sensory stimuli have also been described and appear more convenient to use. In particular, abundant data have been collected on the Generalised Epilepsy Prone Rat (GEPR) which presents convulsive seizures
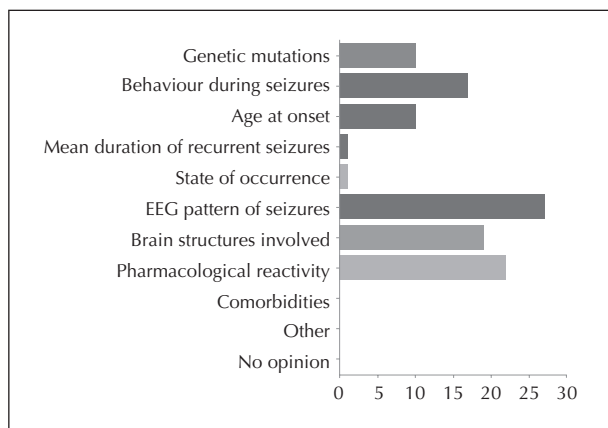
Figure 4. Absence epilepsy. The number of features selected (maximum of three/individual) by 36 clinical experts in epileptology to answer the question: *"In your opinion, what are the most important clinical features that should be present in an animal model, considered by clinicians to be relevant to absence epilepsy?"*

upon stimulation by a loud sound (Jobe *et al.*, 1991). In this model, the pharmacological reactivity offers many similarities with the clinic. However, the type of seizures (mainly tonic) and the structures involved (mainly brainstem) make the data obtained with this model difficult to transpose to human IGE with convulsive seizures or even epilepsies with reflex seizures (Hirsch *et al.*, 1993). New models are being developed in mice which result from different types of gene manipulations, mostly issued from our knowledge on clinical genetics (Frankel, 2009). Although promising, these models will need to be characterised in terms of pharmacological reactivity, EEG patterns, and brain structures involved, in order to provide relevant information for the clinic.

Modelling absence epilepsy

As could be expected, the unique EEG pattern (*i.e.* spike-and-wave discharges) was found to be the most relevant feature to model absence epilepsy by 75% of the clinical epileptologists in the survey (*figure 4*). Similarly, the pharmacological reactivity (61%), as well as the brain structures involved (53%), also clearly emerged as important features. The typical spike-and-wave pattern of absence seizures is an excellent example of an EEG feature that can be objectively measured in several mammalian species. Indeed, spike-and-wave discharges (SWD) were EEG-recorded in all the genetic models that were described during the last 20 years in both mice (Noebels, 1999) and rats (Depaulis and van Luijtelaar, 2005). None of these models display 3-Hz rhythmicity of SWD, as in human patients, but rather 6 to 10 Hz. Whether this is a limi-

tation of these models remains to be demonstrated as there are many other examples where the frequency of neuronal oscillations in rodents is faster than in primates (Depaulis and van Luijtelaar, 2005; Bragin *et al.*, 1999a). The mandatory use of EEG for these models has allowed the rapid identification of the brain structures involved (*i.e.* the cortex and the ventrolateral thalamus) in the initiation and maintenance of the SWD. More recently, the group of van Luijtelaar, as well as our own, identified the somatosensory cortex as the region where SWD are bilaterally initiated in both the WAG/Rij and GAERS models (Meeren *et al.*, 2002; Polack *et al.*, 2007; David *et al.*, 2008). Furthermore, the inhibition of this region clearly suppresses SWD (Polack *et al.*, 2009). Although it is unlikely that the somatosensory cortex *per se* initiates SWD in human patients, the concept of a cortical area of initiation was validated in clinical studies where frontal cortical regions appeared as initiating zones (Holmes *et al.*, 2004; Benuzzi *et al.*, 2012). This concept of "focality" of absence seizures has somewhat challenged the classification of epilepsies based on generalised *versus* focal seizures. It suggests the need to favour models of epileptic syndromes rather than models of epileptic seizures.

The concept of a cortical region initiating SWD has also led to the development of several research projects to understand what makes a cortical neuronal network prone to initiate SWD (Cope *et al.*, 2009; Chipaux *et al.*, 2011). This should lead to the development of new therapeutic targets for absence epilepsy but also for epilepsies associated with SWD and, very likely, for epileptogenesis. Indeed, in both WAG/Rij and GAERS models, a period of several weeks, during which SWD progressively develop, has been described and offers a unique approach to understand the aetiology of this form of epilepsy (Cope *et al.*, 2009). One of the great advantages of these two models is their high pharmacological predictability. In fact, all antiepileptic compounds that suppress SWD in human patients are effective in these two rat models (Depaulis and van Luijtelaar, 2005). In contrast, all AEDs that increase SWD in human patients aggravate absence seizures, suggesting the possibility to predict possible counter-indications when developing a new AED.

WAG/Rij and GAERS models also provide important information on the role of gene mutations that could lead to the development of absence seizures. Different mutations in genes encoding calcium channels have been identified from human patients as well as from different models in the mouse, such as the Tottering, the Lethargic or the Stargazer strains (Noebels, 1999). However, these monogenic models are associated with complex phenotypes that make them difficult to use when developing new AEDs. On the contrary, both WAG/Rij and GAERS models are polygenic with a simpler phenotype (*see below*). In both models, several

quantitative trait loci have been described (Gauguier *et al.*, 2004; Rudolf *et al.*, 2004) but they poorly refer to regions of interest in the human genome. In the GAERS model, a single nucleotide mutation was described in the gene encoding the $Ca_v3.2$ subunit of the low-threshold calcium channel (Powell *et al.*, 2009). This mutation was found in all three current GAERS colonies (Grenoble, Melbourne, and Istanbul) but not in the WAG/Rij strain (Powell, personal communication). The mutation may control alternative splicing of one exon that could be associated with a gain of function of this channel and thus explain about a third of the phenotype. Such a finding is in agreement with the putative mechanisms of action of ethosuccimide, an AED specific for absence epilepsy, and could well lead to the development of new targets for AEDs which can suppress SWD-type seizures. In conclusion, these two rat models offer the ability to study the main features selected by the clinicians in order to understand and treat absence epilepsy. The large amount of data accumulated over the past 20 years may have also influenced the clinicians when answering the survey and it will be interesting to examine whether such a "bias" also exists for clinicians from different countries.

Although this did not appear as a critical issue for the clinicians, WAG/Rij and GAERS models also offer the possibility to study behavioural comorbidities as well as understand the association with absence epilepsy. So far, anxiety- and depression-related behaviours have been shown to be increased in GAERS or WAG/Rij strains when compared to non-epileptic controls (Jones *et al.*, 2010; Sarkisova and van Luijtelaar, 2011). The GAERS strain was also suggested to display behaviour that could be reminiscent of psychosis (Jones *et al.*, 2010). These comorbidities are in fact not very common in children with absence epilepsy which is rather associated with problems in cognitive and neuropsychological function (Conant *et al.*, 2010; Killory *et al.*, 2011; Agati *et al.*, 2012). Future experiments using these two rat models to examine these features may provide information on the relevance to the clinic.

Modelling focal epilepsies associated with cortical dysplasia

According to our survey, histopathology emerged as the most important feature (86%) to model focal epilepsies associated with cortical dysplasia, the most common cause of drug-resistant focal epilepsies in children (Harvey *et al.*, 2008). The EEG pattern of the seizures was also found to be relevant by 58% of the clinicians, whereas most of the other features appeared less critical (*see figure 5*). Indeed, cortical dysplasia has been described as a pathological
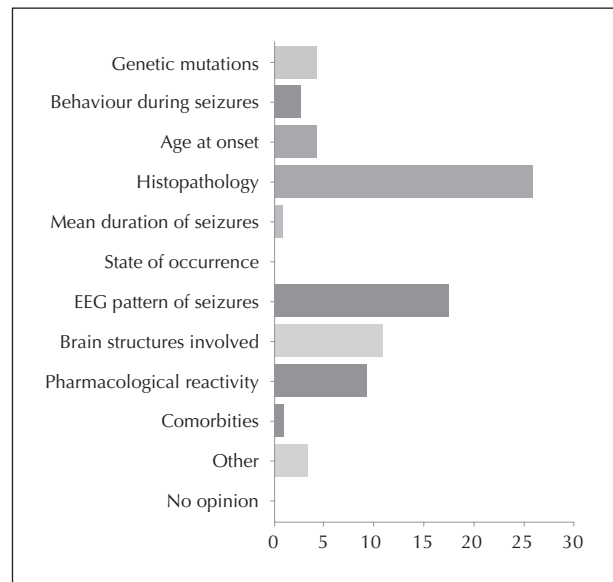

Figure 5. Focal epilepsies associated with cortical dysplasia. The number of features selected (maximum of three/individual) by 36 clinical experts in epileptology to answer the question: "*In your opinion, what are the most important clinical features that should be present in an animal model, considered by clinicians to be relevant to epilepsies associated with cortical dysplasia?*"

substrate for epilepsy (Taylor *et al.*, 1971) and most epilepsies associated with focal cortical dysplasia have a unique EEG pattern (Chassoux *et al.*, 2012). Focal cortical dysplasia is characterised by a disruption of the normal lamination of the cortex and can vary in severity, ranging from a mild disruption of lamination with normal morphology of neurons to a severe loss of laminar organisation. The latter is usually accompanied by the appearance of dysmorphic and misoriented neurons, neuronal clustering, giant neurons, and/or balloon cells (Palmini *et al.*, 2004; Blümcke *et al.*, 2011). Giant neurons apparently have a normal content of cytoplasmic organelles and normally receive symmetric synapses in the cell body and proximal dendrites (Taylor *et al.*, 2001). Balloon cells are "*malformed cells of uncertain origin with large, sometimes multiple, nuclei surrounded by an excess of opalescent, pseudopodic cytoplasm*" (Taylor *et al.*, 1971). Several animal models of cortical dysplasia have been previously described following genetic, foetal, or neonatal manipulation (Sarkisian, 2001). The foetal insult models are induced by administration of an antimitotic drug (methylazoxymethanol acetate or MAM) or by foetal irradiation of pregnant rats. Both methods induce multifocal cortical dysplasia in newborn rats. Prenatal exposure to MAM consistently results in offspring with microcephaly, cortical thinning, multifocal brain malformations, and clusters of misplaced neurons in the hippocampus (Baraban

et al., 2000). One of the most characterised animal models of cortical dysplasia is the *in utero* irradiation model in which offspring develop cortical malformations with a dose-dependent loss of the normal six-layered cortex (Kellinghaus *et al.*, 2004). Genetic animal models also reproduce some rare cortical dysplasia. The telencephalic internal structural heterotopia (TISH) rat model exhibits a forebrain anomaly similar to the human neuronal disorder of double cortex and exhibits spontaneous recurrent electrographic and behavioural seizures (Lee *et al.*, 1997). Other genetic models include the Reeler and Ihara mutant rats. The limitation of these models is the capacity for the mutations in several sets of targeted genes to lead to changes in brain excitability (Sarkisian, 2001). Spontaneous seizures have been observed only in genetic models that showed bilateral or diffuse lesions (Lee *et al.*, 1997).

Type IIB cortical dysplasia (Blümcke *et al.*, 2011) has been characterised by focal loss of cortical lamination, astrogliosis, dysmorphic neurons and glia, and undifferentiated giant cells (analogous to balloon cells). Animal models were generated based on spontaneous or induced mutations of either the *Tsc1* or *Tsc2* genes, mimicking the pathological features of human tuberous sclerosis complex (TSC), with varying degrees. For example, the Eker rat, which carries a spontaneous germline heterozygous mutation of the *Tsc2* gene, exhibits hamartomatous lesions, especially in subcortical or subependymal regions (Yeung *et al.*, 1997; Mizuguchi *et al.*, 2000). Similarly, studies using a number of conditional knockout mice have confirmed selective cytopathological features of TSC, such as disrupted cortical lamination, cytomegalic neurons, and astrogliosis (Uhlmann *et al.*, 2002; Meikle *et al.*, 2007; Way *et al.*, 2009). However, a limitation of these models is the failure to consistently reproduce focal tuber-like lesions.

Although certain pathological aspects of focal cortical dysplasia and TSC can be generated in animal models, does this actually lead to epilepsy? Indeed, animal models display epileptic seizures with great variability. Most of them show evidence of decreased seizure threshold and/or increased neuronal excitability. For example, in MAM rats, a decreased seizure threshold in response to proconvulsant drugs and increased spontaneous or evoked epileptiform activity in hippocampal slices was described (Baraban and Schwartzkroin, 1996; ChevassusAuLouis *et al.*, 1998). More recently, using long-term video-EEG monitoring, spontaneous seizures were observed in irradiation- and MAM-induced models (Kondo *et al.*, 2001; Harrington *et al.*, 2007). However, the incidence of seizures is relatively low with only 10-20% of the animals being epileptic. Similarly, Eker rats have a

slightly increased susceptibility to convulsing agents but have not been documented to display spontaneous seizures (Wenzel *et al.*, 2004), whereas some knockout mouse models of TSC have frequent and progressive seizures (Uhlmann *et al.*, 2002; Erbayat-Altay *et al.*, 2007). Most of these models have a great potential to develop disease-modifying treatments, however, a better characterisation of seizures and reactivity to AEDs is required for developing new compounds.

Modelling focal epilepsies associated with hippocampal sclerosis

It is interesting to note that besides the brain structures involved (61%) and the histopathology (50%), the clinicians considered that the recurrence of focal seizures with *mild* behavioural expression (58%) and the EEG pattern of these seizures (42%) were critical to model mesiotemporal lobe epilepsy. On the contrary, none of them considered that the occurrence of generalised *convulsive* seizures was relevant for this form of epilepsy. In addition, an initial status epilepticus, comorbidities, or the existence of interictal spikes were given low scores, whereas the pharmacological reactivity was found to be important in 19% of the cases (*see figure 6*). These results raise an important issue as it appears somewhat paradoxical that the models that are commonly used to study the physiopathology of temporal lobe epilepsy (*i.e.* systemic injection of kainate or pilocarpine) poorly display the
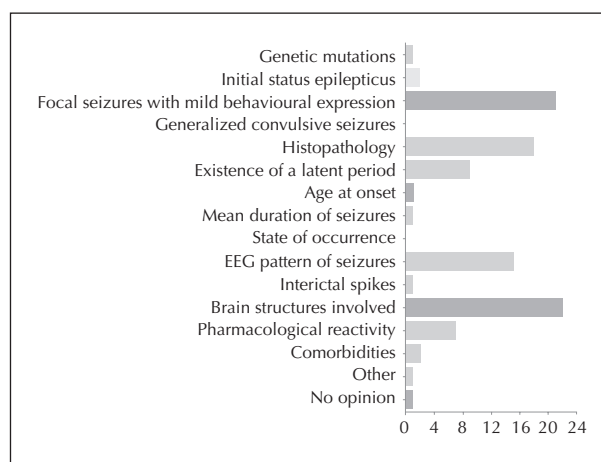

Figure 6. Focal epilepsies associated with hippocampal sclerosis. The number of features selected (maximum of three/individual) by 36 clinical experts in epileptology to answer the question: "*In your opinion, what are the most important clinical features that should be present in an animal model, considered by clinicians to be relevant to temporal lobe epilepsy?*"

features that emerged from our survey. Indeed, in these models, lesions are observed in the hippocampus and limbic structures, but are bilateral and involve other different structures (Navarro Mora *et al.*, 2009). Therefore, the histopathology of these models appears more complex than what is generally reported in the clinic (Williams *et al.*, 2009; Sloviter, 2008; Marchi *et al.*, 2009). More problematic is the fact that *generalised* tonic-clonic seizures are mainly taken into account in these models, whereas focal seizures measured by EEG and/or discrete behavioural signs are rarely quantified. This would appear to be in great contrast to clinical observations where secondary tonic-clonic generalisations are rare in MTLE patients (Cendes *et al.*, 1993). Indeed, MTLE patients suffer from recurrent focal seizures which are most often characterised by an epigastric sensation, impairment of consciousness, oro-alimentary and gestural automatisms, and postictal confusion, associated with focal discharges based on depth-recording (Chabardès *et al.*, 2005). Developing drugs that suppress "generalised" convulsive seizures may thus lead to compounds that are inappropriate for focal seizures without secondary generalisation. There is therefore an urgent need to reconsider our preclinical strategy in order to develop new AEDs that are more adapted to focal seizures, taking into account their specificity.

A few models with recurrent focal (temporal) seizures that require EEG depth recordings have been developed during the last 10 years in mice and rats. They result from the local application of kainate or continuous electrical stimulation that triggers an initial nonconvulsive status epilepticus, *i.e.* which is much less severe than that triggered by systemic injection of pilocarpine or kainate (Riban *et al.*, 2002; Bragin *et al.*, 1999b; Kienzler *et al.*, 2009). This status generally lasts for several hours and does not require pharmacological interruption (*e.g.* injection of diazepam). Among these models, our laboratory has developed and characterised a mouse model of MTLE which is obtained by a unilateral injection of a small dose of kainate in the dorsal hippocampus (Suzuki *et al.*, 1995; Riban *et al.*, 2002). In this model, the nonconvulsive hippocampal status epilepticus is followed by a period of about two weeks, during which recurrent spontaneous hippocampal paroxysmal discharges and hippocampal sclerosis (cell loss, gliosis, mossy fibre sprouting, and granule cell dispersion) progressively develop (Riban *et al.*, 2002; Heinrich *et al.*, 2011). Recently, using *in vivo* intracellular recordings, we showed that during such focal seizures hippocampal neurons display sustained membrane depolarisation on which are superimposed rhythmic depolarisations, supralaminar for action potential discharge with typical paroxysmal depolarization shift (Langlois *et al.*,

2010). As in human patients with MTLE, the recurrent seizures recorded in these mice were mostly confined to the hippocampus and rarely generalised. They were associated with mild behavioural modifications such as chewing, head nodding, or stereotyped grooming (Riban *et al.*, 2002). Finally, in this model, due to the high recurrence of hippocampal discharges, AEDs can easily be tested during the 1-2 hours that follow their injection but also during a chronic treatment. Most importantly, using this model, it is possible to detect the efficacy on focal seizures, rather than generalisation. This may explain why several AEDs are without effects when used for focal seizures, either acutely or after a few days of daily administration (Bressand *et al.*, submitted). Such a pharmacological profile should offer better discrimination between drug candidates for focal epilepsies.

Conclusions

If we aim to discover new AEDs that effectively suppress seizures in refractory epilepsies, we urgently need to reconsider our preclinical strategy and use animal models with features that are as reminiscent as possible to what is observed in human patients. This means taking into consideration not only the seizures, but also other features that characterise the form of epilepsy to be modelled. In this respect, it is important to consider the opinion of hospital neurologists with a strong expertise in epilepsy and drug development, in order to revisit the models that are currently used. In the present study, our survey clearly shows that distinct animal preparations should be used to model the different forms of epilepsy and those with chronic recurrent seizures should be preferred. In addition, the use of EEG to record seizures at the site of onset appears to be mandatory for better determination of the efficacy of a new drug. In addition, it appears more and more unlikely that drugs which are active against generalised convulsive seizures in models suppress focal seizures in human patients. Using animal models with features that are different and/or much more complex than the clinical conditions would appear to be inappropriate and probably misleading, regarding the choice of candidate drugs. Whether additional information, such as associated comorbidities, helps to better design new models, remains an interesting and promising issue. □

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