**PATHOPHYSIOLOGY**

Pathophysiology of epileptic seizures

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Epilepsy represents the most common chronic neurological condition in the dog. As our understanding of the underlying pathophysiology improves, we are better able to describe the neuroanatomical diagnosis, select the best medication for an individual patient and predict the potential for pharmacoresistance to antiepileptic drugs (AEDs). An epileptic seizure is a clinical sign of neurological disease (similar to any other neurological abnormality, such as ataxia or paresis), whereas epilepsy is defined as recurrent epileptic seizures (ie, a patient does not have epilepsy until it has had repeated seizures). Epileptogenesis is the process whereby a seizure focus develops or increases in size, with an associated increase in seizure frequency or severity. While the effect of early instigation of treatment with AEDs on epileptogenesis is still to be elucidated, it is apparent that early treatment results in the development of less long term adverse behaviour effects in the patient. The main risk factors for pharmacoresistance to AEDs include breed (in particular the border collie) and severe or progressively worsening seizures.

EPILEPSY is one of the most widely recognised and studied neurological conditions, with a wealth of detailed descriptions in historical texts. The large number of descriptions in part reflects the complex and multifactorial underlying pathophysiology. The first records providing descriptions of epilepsy date back to Babylonian and Ayurvedic texts from as early as 1500 BC (reviewed by Markel 2011). Originally, epilepsy was attributed to a supernatural force and the term ‘sacred disease’ was applied. However, in 400 BC Hippocrates argued that this disease was no more sacred than any other disease, and correctly postulated that the cause arose within the brain. The term ‘falling disease’ was then more widely accepted and was used in the English language until the late 14th century, when gradually it was replaced by the use of the Greek verb epileptanemai (‘to take hold of or to seize’) in medical texts. This was later converted to the Latin epilepsy and later the Old French, epilepsie, with ‘falling disease’ finally largely being replaced with the term epilepsy following the English translation in 1758 of Rembert Dodoens’ famous Flemish herbal text Cruydeboek.

Today, epilepsy is one of the most important chronic neurological conditions affecting the human population. The prevalence of epilepsy in humans varies between different population groups, but nowhere is it less than 3 cases per 1000 of population, and in some regions is as high as 40 cases per 1000 of population (Joint Epilepsy Council 2011). In the UK, the prevalence of epilepsy is estimated as 9.7 cases per 1000 of population, and the incidence is estimated at 0.51 cases per 1000 of population per year (Joint Epilepsy Council 2011). Within the canine population, epilepsy is described as the most important chronic neurological condition affecting dogs, with a prevalence estimated at between 0.5 per cent to 5.7 per cent of the population, depending on the individual study and dog breed (reviewed in Chandler 2006).

**Definitions**

As part of the approach to the case with epileptic seizures, it is important to correctly understand the associated terminology. Epilepsy and epileptic seizures are (similar to ataxia or paresis) clinical signs of neurological disease and do not represent a diagnosis as such. Patients presenting with epileptic seizures may have a large number of potential underlying causes. However, the situation is slightly complicated in that the term epilepsy is on occasion also used as part of the diagnosis, for example, idiopathic epilepsy also referred to as ‘presumed genetic epilepsy’ or post-traumatic epilepsy. Where a syndrome is well described, then the use of the term epilepsy as part of the diagnosis may be acceptable, but it is important to remember that in most cases epilepsy refers to a clinical presentation, and that the clinical presentation may have a variety of different causes.

**Seizure**

The term seizure [derived from the Latin sacire, meaning ‘to seize’ or ‘take possession of’] is widely used to describe epileptic seizures and describes the clinical manifestation of an abnormal, excessive, hypersynchronous discharge of a group of neurons within the cerebral cortex. The exact clinical manifestation will depend on the region of the cerebral cortex affected and whether the seizure generalises to affect the entire forebrain.

**Epilepsy**

Epilepsy describes recurrent seizures (ie, a dog is only affected by epilepsy when it has more than one epileptic seizure). In some situations, the use of the term epilepsy is limited to those conditions where there is not an underlying acute toxic, metabolic or central nervous system (CNS) insult. Differentiating between seizures and epilepsy is also important. In the case of a single, isolated seizure, the emphasis is on the investigation and treatment of the underlying cause (with the potential for emergency management if the seizure is prolonged). For epilepsy, the management is more likely to require chronic therapy with antiepileptic drugs (AEDs). Recurrent seizures also have different consequences for the owner and pet, and may impact substantively on the health, behaviour and quality of life of an affected dog and/or its owner.

**Epileptogenesis**

Epileptogenesis details the process whereby a normal neuronal network is converted into a hyperexcitable neuronal network. In some conditions, for example, post-traumatic epilepsy, the onset of the epileptic seizures may be delayed for some time after the brain injury or disease, or may not develop at all. Following head trauma, the likelihood of post-traumatic epileptic seizures increases with the degree of damage to the cerebral cortex (increasing dependent on whether there is just head injury, whether there are skull fractures, through to cases with direct brain injury affecting the cerebral cortex). However, not all of these cases will develop epileptic seizures, and in those that do the onset may be some months to years after the initial brain injury. Although the injury is
One component of the cerebral cortex

Epileptogenesis was best described in an animal kindling model (Goddard 1967), where daily, subconvulsive stimulation of defined brain regions resulted in the eventual development of stimulation-induced epileptic seizures, and in some animals, even spontaneous epileptic seizures. These alterations in brain region excitability were permanent and subsequent studies have demonstrated a variety of changes, including selective neuronal loss, axonal reorganisation and altered glutamate channel properties. These findings are used to explain the increase in epileptic seizure frequency and severity, which occurs over time in many human and animal patients.

Cellular organisation of the cerebral cortex: inhibitory and excitatory neurons

Epileptic seizures arise within the forebrain (Fig 2), of which the cerebral cortex and the thalamus are major components. One component of the cerebral cortex that is commonly implicated in epileptic seizures, particularly in human patients, is the hippocampus, and alterations in the hippocampus in dogs are increasingly being recognised as a consequence of epileptic seizures.

The grey matter of the cerebral cortex is a relatively thin layer of only a few millimetres arranged on the surface. The separation of neuronal cell bodies (making up the grey matter) from the axonal processes (making up the white matter) allows conservation of space with shorter axonal processes. The cerebral cortex grey matter is further divided into a number of different layers or 'sheets' of neurons (varying from three to six layers of neurons). Neurons performing similar functions have a requirement for communication, and this is more efficient if these communications are over short distances. Neurons sharing similar functional properties (e.g., neurons involved in vision and which share the same receptive field in the same region of the retina are therefore adjacent and layered with their axonal projections in a radial column which extends through the layers of the cerebral cortex.

The cerebral cortex comprises two general classes of neurons: the projection or principle neurons and the interneurons. The projection neurons (for example, the pyramidal neurons) project or transmit information to distant neurons and are mainly excitatory in function. Interneurons (for example, the basket cells) have local projections with mainly an inhibitory function. Interneurons are very important for local inhibition, in particular the formation of inhibitory feedback loops: when a projection neuron synapses on a local inhibitory neuron, which in turn synapses back on the projection neuron. More recent evidence suggests that interneurons may also have some extensive or distant projections and that these interneurons may be responsible for strong synchronisation or pacing activity to a pool of projection neurons.

Major inhibitory and excitatory central nervous system neurotransmitters

The basic response of a neuron to stimulation is the generation of an action potential, with resultant propagation of the depolarisation along the axon and release of neurotransmitter at the axon terminal. However, the action potential is an all-or-nothing response, and the likelihood of a stimulus resulting in sufficient depolarisation to induce an action potential depends on the local neuronal environment. In patients with epilepsy, the ambition is to avoid the creation of a hyperexcitable state, which can result from increased excitation, decreased inhibition, a change in the voltage-gated ion channels or a change in the intracellular or extracellular ion concentrations towards a more depolarised state.

The main neurotransmitters within the CNS include glutamate, gamma-amino-butyric acid (GABA), noradrenaline, serotonin, acetylcholine, dopamine, histamine and some other neuropeptides and hormones. Of these, glutamate is the major excitatory neurotransmitter and GABA the major inhibitory neurotransmitter.

Potentiation of glutamate or using a glutamate receptor agonist has been shown to promote seizure activity, while the use of glutamate antagonists reduces seizure activity. There are a variety of subtypes of glutamate receptors and these are subdivided on whether they are ionotropic (i.e., open to become permeable to cations, and are differentiated on the basis of their individual cation permeability) or metabotropic (i.e., function by means of membrane associated G-proteins – G-proteins function as a molecular ‘switch’ to transmit a stimulus from outside the cell membrane to inside the cell). The major ionotropic glutamate receptors include AMPA, kainite and NMDA receptors and all are permeable to Na⁺ and K⁺. The NMDA receptor is also permeable to Ca²⁺ (mediated by Mg²⁺) and it is this mechanism that is responsible for excitotoxicity following excessive neuronal activation (in conditions such as severe epileptic seizures) through Ca²⁺-mediated neuronal injury (Fig 3).
GABA is the major inhibitory CNS neurotransmitter. The two main GABA receptors are GABA_A, which are located postsynaptically, and GABA_B, which are located presynaptically. Stimulation of the GABA_A receptor makes it permeable to Cl^- ions, with an influx of Cl^- ions into the cell. This influx hyperpolarises the cell and makes it more stable and less likely to reach the threshold for depolarisation required to generate an action potential. GABA_A receptor agonists, such as barbiturates and benzodiazepines, therefore reduce seizure activity. GABA_B receptor agonists do not result in Cl^- release, but rather restrict neurotransmitter release due to their presynaptic location. GABA_B receptors agonists therefore may induce a hyperexcitable state and seizure activity.

**Generation and propagation of focal and generalised epileptic seizures**

The exact mechanisms underlying seizure generation in the brain are still not fully understood, in particular how defined populations of cells become hyperexcitable. The laminar arrangement of the cerebral cortex and the organisation of radial columns of functionally related neurons may contribute to the formation of groups of pacemaker neurons acting as a seizure focus. Within these populations of neurons, selective loss of interneurons may take place, which reduces the normal feedback inhibition of projection neurons. Alternatively, axonal sprouting and consequent synaptic reorganisation following injury or disease may create new excitatory synapses between adjacent interneurons. A different theory that has been proposed is that loss of projection interneurons may result in a reduction in inhibitory neurotransmission. These different mechanisms of seizure generation very likely occur in combination.

**Focal seizures**

Focal seizures (partial seizures or localised seizures) are restricted to one cerebral hemisphere and usually to a single focus within this cerebral hemisphere. The clinical manifestation of a focal seizure will vary according to the location of the seizure focus. Focal seizures usually do not demonstrate loss of consciousness (simple partial seizure), but in some cases may affect a large part of the one cerebral hemisphere with impairment of consciousness (complex partial seizure).

**Generalised seizures**

Generalised seizures affect both cerebral hemispheres and are associated with an impairment of consciousness (typically a loss of consciousness), with the most common type in dogs being a generalised tonic-clonic seizure.

**Seizure propagation**

Once a synchronous seizure discharge has developed within the isolated pacemaker population of neurons (focal seizure), there is usually rapid dissemination vertically and horizontally to incorporate adjacent cortical regions (secondary generalisation). This dissemination of the synchronous seizure discharge is usually prevented by a region of surrounding inhibition mediated by inhibitory neurons. However, if there is sufficient activation then surrounding neurons are incorporated as a result of an increase in extracellular K+ (which depolarises adjacent neurons), Ca++ accumulation in presynaptic terminals (enhancing neurotransmitter release) and activation of excitatory NMDA receptors as a consequence of the depolarisation.

Mapping of the seizure focus or origin is important in human patients demonstrating pharmacoresistance as it allows the opportunity for surgical excision of the seizure focus, and thereby the possibility for improvement in epilepsy control (usually going from an AED non-responder to a responder, but in some cases even complete seizure remission).

Epileptic seizures may also appear to arise from the entire cerebral cortex simultaneously (generalised seizures). The mechanism underlying this process is unclear. Consistent with the saying ‘sleep and epilepsy are bedfellows’, one of the most frequent times when dogs with epilepsy demonstrate seizures is during sleep. One potential explanation for this is that sleep-like, cortically generated oscillations may progress directly into hypersynchronous seizure discharges.

**Termination of epileptic seizures**

The majority of seizures are self-limiting, if they do not terminate spontaneously then these seizures are defined as status epilepticus. The mechanisms underlying the spontaneous termination of seizures are likely to be multifactorial and include both cell-intrinsic factors, local cellular environment factors and mechanisms acting remotely to prevent seizure spread. It has been shown in human patients that seizure duration is relatively short in adult patients, but are considerably longer in children, suggesting that different mechanisms are responsible for seizure termination in the developing versus developed brain, or that these mechanisms are not yet fully developed in children. The cell-intrinsic mechanisms for the termination of seizures include changes in the intracellular and transmembrane ion current gradients due to repeated
depolarisation, reduced coupling of adjacent neurons due to impairment of gap junctions (as a result of the altered ion concentrations) and depletion of local energy supplies. The local cellular environment factors responsible for termination of seizures are numerous, but the major ones include depletion of glutamate, uptake of presynaptic glutamate by glial cells, development of local acidosis (either intracellular or extracellular), enhancement of GABA activity by stimulation of interneurons, uncoupling of cellular networks by modulation of gap junctions and changes in other neuromodulators and peptides. The remote mechanisms responsible for seizure modulation include vagal stimulation and activity of the basal nuclei.

**Effect of epileptic seizures on the owner and dog**

There are two considerations when a dog presents following an epileptic seizure: the effect on the dog of the seizure (both the immediate post-seizure effects, but also longer-term effects on the dog’s quality of life), and the effect on the owner of witnessing an epileptic seizure in their pet and living with a pet with epilepsy. There are only limited studies evaluating the effect on an owner of witnessing a seizure in their pet, although these are relatively well described for human patients. The memory and memorability of witnessing an epileptic seizure event in a human patient is substantial, even if the patient is not closely related to or known by the observer. In one study, the emotional importance rating for someone observing an epileptic seizure in a human patient was categorised as very high and the event was rated as very important (Aydemir and others 2009). Both the observer and the patient rated the seizure event as very surprising. When owner perceptions of seizures in dogs were examined using YouTube, it was interesting to note that people either made derogatory or sympathetic comments, but that the public perception of epilepsy in dogs was more favourable than in humans. Around 50 per cent reported that the seizures in dogs appeared ‘funny’. Owners of dogs with epilepsy frequently used YouTube to seek information and help from other pet owners (Preston and others 2013).

Immediately following an epileptic seizure, temporary, mild neurological deficits may manifest themselves as a consequence of the epileptic seizure (Fig 3). These post-seizure effects occur irrespective of the underlying cause of the seizure and are termed ‘postictal depression’. These effects are usually temporary and resolve after a few hours, but can be equally distressing to the owner and may include a combination of reduced recognition of the owners and surroundings, sedation, ataxia, apparent blindness and deafness and altered behaviour. The longer or more severe the seizures are, then the longer the postictal depression may last, particularly after severe cluster seizures or status epilepticus.

In the longer term, the development of epilepsy in a dog may also have additional

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**Fig 3**: Post-seizure changes on MRI following a severe epileptic seizure episode (arrowed). T2-weighted images, dorsal (a), transverse at the level of the interthalamic adhesion (b) and transverse at the level of the colliculi (c)

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**Fig 4**: Obstructive hydrocephalus as a cause of symptomatic epilepsy. There is marked distention of the entire ventricular system, attenuation of the cerebrospinal fluid signal in the subarachnoid spaces around the brain and periventricular oedema (arrowed on [d]). T2-weighted sagittal (a), dorsal (b) and transverse (c) and FLAIR transverse (d) magnetic resonance images
seizures are not a diagnosis per se, but rather a clinical sign of neurological disease. The presence of epileptic seizures implies a forebrain disorder, and as such the assessment concentrates on evaluation of the forebrain. However, the cause of epileptic seizures may originate outside (extracranial), usually with symmetrical neurological deficits if present, or inside (intracranial) the brain. Intracranial causes may be further subdivided into functional disorders, where no gross structural changes are evident in the brain and therefore usually no neurological deficits are evident in the interictal period, and structural disorders, where there is a gross structural cause for the seizures within the brain, for example, a brain tumour, and which often have asymmetrical neurological deficits.

On the basis of the neuroanatomical localisation, seizures can be classified according to their cause as idiopathic epilepsy, symptomatic epilepsy, reactive epilepsy and cryptogenic epilepsy. However, there are limitations to this classification system, many causes of seizures are multifactorial whereas the classification system only considers one cause; the cause is dependent on the amount of investigation performed, and there is no consideration given to epileptogenesis. It may be more useful to consider the mechanism that gives rise to the development of seizures and how this can be manipulated.

Idiopathic epilepsy
Idiopathic epilepsy is the most common cause of epileptic seizures in the dog and can be predicted with a 95 per cent probability if the seizure onset is between six months and six years of age, the physical and neurological examination is normal, there is normal blood work and the dog is demonstrating generalised tonic-clonic seizures (Smith and others 2008). Idiopathic epilepsy most likely has an underlying genetic cause and as such is also referred to as ‘presumed genetic’, particularly in human medicine. In idiopathic epilepsy, there are no gross neuroanatomic or neuropathological abnormalities to explain the seizures [see the article on idiopathic epilepsy on pp 17-23].

Symptomatic epilepsy
Epileptic seizures occur as a clinical sign of underlying brain disease evident as an anatomical or pathological abnormality. This may also include genetic causes where the underlying genetic defect has been characterised. The causes of symptomatic epilepsy can be inherited (e.g., L-2-hydroxyglutaric aciduria in the Staffordshire bull terrier), congenital (e.g., hydrocephalus) [Fig 4] and acquired (e.g., secondary to a brain tumour or post-traumatic epilepsy). There are usually other clinical signs of brain disease in these cases, and if present these other neurological deficits are frequently asymmetrical.

Reactive epilepsy (or provoked) epilepsy
Reactive epilepsy occurs in response to a specific environmental (e.g., toxic) or systemic factor (e.g., metabolic disease such as a portosystemic shunt [Fig 5]) and where there is no gross causative neuroanatomic or neuropathological abnormality. The causes may be varied and includes some genetic causes.

Cryptogenic epilepsy
Cryptogenic epilepsy is defined as presumed symptomatic epilepsy, but where an underlying cause cannot be identified. This is an important cause of seizures in adult human patients, but the number of cases is diminishing with improved diagnostic capabilities. Cryptogenic epilepsy is sometimes incorrectly used in veterinary medicine to define cases with idiopathic epilepsy, but where the seizure onset is over six years of age. However, idiopathic epilepsy can occur in dogs over six years of age. Dogs with generalised tonic-clonic seizures with a seizure onset of over six years of age, and with no clinical, haematological, biochemical or neurological abnormalities, still have a probability of a normal MRI and cerebrospinal fluid examination of 70 per cent.

Importance of treatment in epilepsy and the avoidance of epileptogenesis
It has been suggested that human patients with epilepsy have better long-term control when the antiepileptic medication is started after the first epileptic seizure. However, when this was examined in developing countries (where antiepileptic drugs are not widely available and therefore treatment is often not initiated or is initiated later in the disease course), the rates of remission for epilepsy were equivalent to those in more developed countries (where treatment is initiated earlier) [Placencia and others 1993]. It is likely that canine epilepsy is a progressive disease, with increasing seizure frequency over time in dogs not on treatment [Loscher and others 2004], and this may provide some...
Pathophysiology of pharmacoresistance in canine epilepsy

A wide variation in the drug-responsiveness in canine epilepsy has been demonstrated between different dog breeds, and between dogs within the same breed. These are still poorly understood, but we now understand some of the genetic and clinical risk factors and are better able to predict outcome in individual dogs. Where a dog demonstrates a poor response to a particular AED, the term used to describe this is pharmacoresistance.

Defining pharmacoresistance

For an AED to be defined as effective in an individual patient, there should be at least a 50 per cent reduction in seizure frequency, as compared to before starting medication. Ideally, the improvement would be greater than this and would also result in a reduction in the severity of the seizure episodes. However, in most cases, the decision of whether a dog is controlled or not is decided by the owner and it is essential that they are well informed, to be able to accurately assess their dog’s seizure control. When seizure control is assessed in dogs with idiopathic epilepsy, more than two thirds of these dogs will continue to have epileptic seizures (Heynold and others 1997, Arrol and others 2012) and around one-third of these dogs will remain inadequately controlled (less than 50 per cent reduction in seizure frequency) (Schwartz-Porschen and others 1985, Podell and Fenner 1993, Trepnian and others 1998). While we need to remember that these dogs represent a referral population, and therefore may be biased towards a more severe phenotype, it does highlight the problems associated with achieving good seizure control in dogs with idiopathic epilepsy. If we ignore the definition of what describes an effective AED (more than 50 per cent reduction in seizure frequency) and look at owner perceptions, around one-third of dog owners feel that only complete seizure control, others tolerate one seizure every three to six months (Wessmann and others 2012). It is therefore likely that many owners will not be satisfied if their dog has a high frequency of seizures (even if this frequency is reduced when compared to before starting medication), or even if their dog has a relatively low seizure frequency.

Genetic risk factors for pharmacoresistance in canine epilepsy

It is widely accepted that the most likely underlying cause of idiopathic epilepsy is a genetic defect, and an alternative term which is often used (particularly in human patients) is presumed genetic epilepsy. In addition to a probable genetic cause for epilepsy, genetics may also play a role in determining the response to a particular AED in an individual dog. This is best described in the border collie, where not only may they present with a particularly severe form of epilepsy (characterised by cluster seizures and a high seizure frequency), they are also more likely to demonstrate pharmacoresistance to phenobarbital had a single nucleotide polymorphism in the promoter region of the multidrug transporter gene encoding for P-glycoprotein, potentially changing the expression of P-glycoprotein at the blood-brain barrier and altered transport of phenobarbital (Alves and others 2011). However, this finding has not been replicated in the related Australian shepherd dog (Weissl and others 2012) and a subsequent study has suggested that there may be a variety of genes associated with altered drug responses to phenobarbital (Kennerly and others 2009). It is likely that the genetics of pharmacoresistance for AEDs is multifactorial, but it does raise the possibility of individually tailored AED protocols on the basis of genotype.

Clinical risk factors for pharmacoresistance in canine epilepsy

Clinical risk factors for pharmacoresistance, which have been demonstrated in dogs, rodents and humans, are mainly those of epilepsy severity (high seizure frequency, cluster seizures and status epilepticus all being correlated with poor long term control). Increasing severity of epilepsy is significantly associated with the development of pharmacoresistance to AEDs (Heynold and others 1997, Löscher and Brandt 2010). An onset of epilepsy at less than a year of age is also associated with a worse long term prognosis, although beyond this age there are varying conclusions from different studies, and age of onset of epileptic seizures may be less of a consideration in the dogs over one year of age (Heynold and others 1999, Arrol and others 2012).

Summary

When presented with a patient with a suspected epileptic seizure, it is essential to first define whether the episodes truly represent epileptic seizures. Once you are satisfied that they do, the next step is to ascertain whether they are focal or generalised seizures and if the dog has concurrent clinical or neurological deficits. Classification of the epileptic seizures on the basis of neuroanatomical diagnosis is essential in order to plan the further investigation and to design an appropriate therapeutic strategy: this may comprise symptomatic control of the epileptic seizures, or treatment of the underlying cause, or both. Idiopathic epilepsy represents the most common cause of epileptic seizures in the dog, but other seizure classifications include symptomatic epilepsy (secondary to a neuroanatomical or neuropathological brain lesion), reactive epilepsy (secondary to a systemic or environmental disorder) and cryptogenic epilepsy (presumed symptomatic but testing has failed to demonstrate the cause). Finally, we are becoming increasingly more accurate in our ability to predict the response to AED treatment in individual cases, in particular the risk of developing pharmacoresistance.

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