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Review

The influence of sex hormones on seizures in dogs and humans

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ABSTRACT

Epilepsy is the most common chronic neurological disorder in both humans and dogs. The effect of sex hormones on seizures is well documented in human medicine. Catamenial epilepsy is defined as an increase in frequency and severity of seizures during certain periods of the menstrual cycle. Oestradiol increases seizure activity and progesterone is believed to exhibit a protective effect. The role of androgens is controversial and there is a lack of research focusing on androgens and epilepsy. Indeed, little is known about the influence of sex hormones on epilepsy in dogs. Sterilisation is believed to improve seizure control, but no systematic research has been conducted in this field.

This review provides an overview of the current literature on the influence of sex hormones on seizures in humans. The literature on idiopathic epilepsy in dogs was assessed to identify potential risk factors related to sex and sterilisation status. In general, there appears to be an over-representation of male dogs with idiopathic epilepsy but no explanation for this difference in prevalence between sexes has been reported. In addition, no reliable conclusions can be drawn on the effect of sterilisation due to the lack of focused research and robust scientific evidence.

Introduction

Epilepsy is the most common chronic neurological disorder in humans and dogs with an estimated prevalence in dogs of about 1–2% in a referral hospital population (Schwartz-Porsche, 1986) and 0.6% in first opinion practice (Kearsley-Fleet et al., 2013). Higher prevalences (up to 18%) have been reported in breed-specific studies (Jaggy et al., 1998; Kathmann et al., 1999; Berendt et al., 2002; Casal et al., 2006; Gulløv et al., 2011). The dog has been proposed as a spontaneous disease model for humans and, conversely, the human epileptic patient could represent a good model for dogs (Löscher, 1997; Chandler, 2006; Shihab et al., 2011). Dogs and humans have a similar seizure phenomenology and both species live in the same environment with potential exposure to similar external factors (Berendt et al., 2004; Chandler, 2006; Shihab et al., 2011).

Epileptic seizures in veterinary medicine traditionally are divided into three groups based on aetiology, namely, idiopathic, symptomatic and reactive. Idiopathic, also called primary epilepsy, is defined as having chronic recurring seizures with no identifiable brain abnormality. In symptomatic or secondary epilepsy, a structural cause is identified in the brain. Reactive seizures refer to systemic metabolic or toxic conditions causing seizures. The term cryptogenic (presumed symptomatic) epilepsy is rarely used in veterinary medicine. It is widely held that idiopathic epilepsy has a strong hereditary basis. This is reflected in the new classification of epilepsy in human medicine into genetic, structural-metabolic and unknown cause (formerly idiopathic, symptomatic and cryptogenic, respectively) (Berg et al., 2010; Berg and Scheffer, 2011).

Genetic factors are a main focus of interest in the study of epilepsy in humans and veterinary species. However, the exact genetic basis of most cases remains unknown (Shorvon, 2011a,b; Ekenstedt et al., 2012). Identification of a causative gene mutation in canine epilepsy has been successful in familial juvenile epilepsy in Lagotto Romagnolo dogs (Lohi et al., 2009; Seppälä et al., 2011) and in the case of autosomal recessive progressive myoclonus epilepsy in miniature wire-haired Dachshunds (Lohi et al., 2005). A risk-conferring locus has also been identified in idiopathic epilepsy in Belgian Shepherd dogs (Seppälä et al., 2012).

A better understanding of epigenetic and epistatic mechanisms in neurodevelopment, and not simply continuing searches for genetic polymorphisms, may help future advances. Other factors such as sex hormones may play an important role in understanding the pathophysiology of idiopathic epilepsy (Shorvon, 2011a,b; Ekenstedt et al., 2012). Idiopathic epilepsy is a chronic condition, which has an impact on the quality of life of owners and their pets and on the lifespan of dogs (Chang et al., 2006; Berendt et al., 2007). Most dogs benefit from antiepileptic drugs (AEDs), but up to 80% of dogs in referral hospital populations continue to have seizures (Arrol et al.,

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2012). Therefore, factors in addition to standard AEDs should be explored to improve survival and quality of life in dogs with idiopathic epilepsy.

In humans, the effects of sex hormones on seizures and epilepsy are well documented. Catamenial epilepsy is defined as changes in seizure frequency and severity over the course of the menstrual cycle. This phenomenon has been attributed to the neuroactive properties of steroid sex hormones and the cyclic variation of their serum levels (Bäckström, 1976a,b; Herzog et al., 1997). Oestradiol has been shown to increase seizure activity. It induces structural and functional changes in hippocampal neurons which may contribute significantly to an increase in seizure susceptibility (Woolley and Schwartzkroin, 1998; Frye, 2008; Herzog, 2008). In contrast, progesterone is believed to protect the brain against seizures (Woolley and Schwartzkroin, 1998; Frye, 2008; Herzog, 2008).

The role of androgens is controversial; they were found to be proconvulsant in some experimental models (Mejías-Aponte et al., 2002; Mróz et al., 2009), whereas recent studies have shown a protective effect of testosterone against seizure development (Mejías-Aponte et al., 2002; Rhodes and Frye, 2004; Mróz et al., 2009). Overall, less research has focused on the effects of male hormones due to their lack of major fluctuations (Frye and Rhodes, 2009), and most experimental studies have been performed in rodents and not in dogs.

To date, an association between seizure frequency and severity with sex or sterilisation status has not been scientifically demonstrated in dogs (Monteiro et al., 2012). Dog owners and particularly the dog breeding community, however, perceive that sex and sterilisation might have an effect on seizure control. Data published on the effects of sex hormones in dogs with idiopathic epilepsy are probably biased due to the common habit of sterilising pet dogs early in life in many developed countries.

The purpose of this review is to examine published data on the relationship of sex hormones and epilepsy. We further assess the literature on canine idiopathic epilepsy to identify potential risk factors related to sex and sterilisation status.

Studies in humans: sex steroids and seizures

The hypothalamic–pituitary–gonadal axis

The release of sex steroid hormones is controlled by the hypothalamic–pituitary–gonadal axis. The interaction between the sex steroid hormonal axis, epilepsy, and the medication used to treat epilepsy is complex (Pennell, 2009) (Fig. 1). Ictal activity can have profound negative effects on the function of the hippocampus in terms of disruption of the hypothalamic regulation of pituitary secretion, resulting in alteration of gonadal function (Mejías-Aponte et al., 2002; Rhodes and Frye, 2004). Likewise, stress hormones (e.g. cortisol) have an impact on neuronal excitability and seizure susceptibility (Maguire and Salpekar, 2013).

Neurobiology of sex steroids

Steroid hormones have several different activities in the central nervous system (CNS). Steroids bind to intracellular steroid receptors (genomic mechanism), but can also produce rapid effects on neuronal excitability and synaptic function through direct interactions with membrane targets, such as ligand-gated ion channels and neurotransmitter transporters. Interactions with the intracellular receptors modulate gene transcription with a response time in the order of several minutes, hours or days, in contrast to the interactions with membrane targets, where effects can occur within seconds to minutes (Frye, 2008; Herzog, 2008).

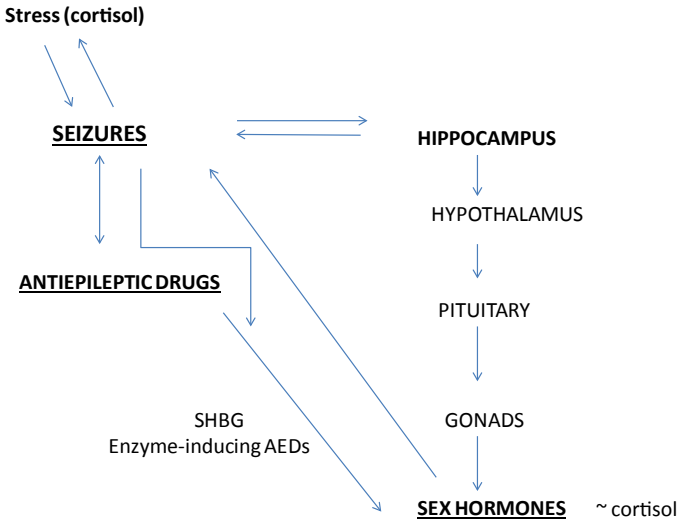

Fig. 1. Diagram of multi-directional interactions between seizures, hippocampus, anti-epileptic drugs (AEDs), and sex hormones. SHBG, sex hormone binding globulin.

Oestradiol affects neuronal excitability by cytosolic neuronal oestrogen receptor-mediated genomic dependent mechanisms (Woolley and Schwartzkroin, 1998; Herzog, 2008). Oestradiol also has a direct excitatory effect at the neuronal membrane where it augments N-methyl-D-aspartate (NMDA)-mediated glutamate receptor activity. This enhances the resting discharge rates of neurons in a number of brain areas, including the hippocampus, which is a key brain structure for cognition and emotional balance and the generation and propagation of seizures (Woolley and Schwartzkroin, 1998; Herzog, 2008).

At the cellular level, oestradiol increases the numbers of hippocampal cornu ammonis (CA1) pyramidal cell spines and excitatory synapses and decreases seizure threshold (Woolley and Schwartzkroin, 1998; Pennell, 2009). Changes to the dendritic morphology which increase pyramidal cell spines, aberrant excitatory synaptogenesis and sensitisation are a common feature, underlying and interlinking both mood disorders and seizures. Hence, studies on depression in women confirmed a relationship between oestrogens and hippocampal synaptogenesis (Hajszan and MacLusky, 2006). Dogs also suffer behavioural changes due to the effect of seizures on hippocampal function, but no data are available on differences between intact and sterilised female dogs (Shihab et al., 2011). One might suspect intact female dogs to be more prone to these effects due to the higher levels of oestrogens.

Progesterone can act via genomic mechanisms to lower oestrogen receptor expression and thereby antagonise oestrogen actions. Progesterone and particularly some of its neuroactive metabolites, most notably allopregnanolone (ALLO), also exert direct membrane-mediated inhibitory effects by potentiating γ-aminobutyric acid $(GABA)_A$-mediated chloride conductance, which results in decreased hippocampal neuronal excitability as well as potentiating the activity of the inhibitory substance adenosine and diminishing nicotinic acetylcholine receptor-mediated conductance (Woolley and Schwartzkroin, 1998; Herzog, 2008; Pennell, 2009).

Male androgens exert their neuroactive effects through both genomic effects through intracellular androgen receptors and 'non-genomic' effects (Frye and Rhodes, 2009). However, less research has been carried out on the effects of male hormones on CNS activity because of their lack of major fluctuations in man.