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The neuroendocrine basis of sex differences in epilepsy

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ABSTRACT

Epilepsy affects people of all ages and both genders. Sex differences are well known in epilepsy. Seizure susceptibility and the incidence of epilepsy are generally higher in men than women. In addition, there are gender-specific epilepsies such as catamenial epilepsy, a neuroendocrine condition in which seizures are most often clustered around the perimenstrual or periovulatory period in adult women with epilepsy. Changes in seizure sensitivity are also evident at puberty, pregnancy, and menopause. Sex differences in seizure susceptibility and resistance to antiseizure drugs can be studied in experimental models. An improved understanding of the neuroendocrine basis of sex differences or resistance to protective drugs is essential to develop targeted therapies for sex-specific seizure conditions. This article provides a brief overview of the current status of sex differences in seizure susceptibility and the potential mechanisms underlying the gender differences in seizure sensitivity.

1. Introduction

Epilepsy has many causes. Sex differences are well known in epilepsy, which is characterized by an enduring predisposition to recurrent seizures. A seizure is an abnormal electrical storm in the brain that causes sudden alterations in consciousness, sensation and behavior that can manifest in forms ranging from an eye flicker to full-body convulsions. Epileptic seizures arise from dysfunctional neuronal network mechanisms that regulate excitability and synchrony. Epileptic seizures are classified into partial (simple partial and complex partial) and generalized (absence, tonic-clonic, myoclonic, and atonic seizures) types. Every year, nearly 150,000 new cases of epilepsy are diagnosed in the United States (Hesdorffer and Begley, 2013). Despite the availability of many medications, nearly 30% of people with epilepsy have refractory seizures that do not respond to any of the currently available treatment options.

Catamenial epilepsy is a type of gender-specific epilepsy in which seizures are clustered around a particular phase of the menstrual cycle. This condition affects as many as 70% of women with epilepsy (Reddy, 2003, 2016a). Most of these patients suffer from uncontrollable seizures, which could damage the brain and adversely impact their quality of life. Therefore, there is a large gap in our understanding of sex differences in epileptic seizures and symptomatic antiepileptic medications' control of a disease with no cure. Epilepsy can be either caused by certain genetic defects or acquired from a predisposing brain injury. Consequently, there are several experimental models that capture a few of these features. Sex differences are also evident in experimental models of seizure susceptibility and epileptogenesis, which occurs following a precipitating insult or injury, such as traumatic brain injury, stroke, neurotoxicity, brain infections, or prolonged seizures (Reddy, 2009a, 2013a, 2013b). In 2014, the NIH issued a policy about the inclusion of both genders in the preclinical research (Clayton and Collins, 2014). This article provides a brief overview of the current status of sex differences in epilepsy and the potential mechanisms underlying the sex differences in seizure sensitivity.

2. Sex differences in clinical epilepsy

The issue of sex differences in seizure susceptibility has been longstanding in the study of epilepsy. Clinical evidence shows gender- and age-related expression in many seizure syndromes. The incidence of epilepsy is generally higher in males than in females; however, the prevalence depends a lot on the specific form of epilepsy (Hauser, 1997; Christensen et al., 2005). More women than men are diagnosed with idiopathic generalized and cyptogenic localization-related epilepsies, but localization-related symptomatic epilepsies are more frequent in men (Hauser, 1997; Christensen et al., 2005). In general, men are more susceptible to injury-induced seizures than women. Additionally, there is a higher frequency of infantile spasms, an age-specific epileptic syndrome affecting infants and young children, in boys than girls. Furthermore, some findings have shown that in early-onset temporal lobe epilepsy, women show greater functional plasticity for verbal memory than men. The relationship between menstrual cycle and seizure sensitivity in women is well known and is greatly influenced by hormonal fluctuations associated with menstrual cycle phases. However, a recent review yielded no consistent evidence of gender differences in the incidence or consequences of these epilepsies (Perucca et al., 2014).

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Nevertheless, there is considerable evidence indicating that males exhibit greater seizure susceptibility, while many females exhibit greater fluctuations in susceptibility to seizures, including menstrual cycle-related changes in seizure activity.

Growing literature also suggests that the incidence of epilepsy differs between men and women (Savic and Engel, 2014). In most countries, not only is the incidence of epilepsy lower in women than men, but it has also been reported that males have a higher lifetime risk of developing epilepsy (Sridharan and Murthy, 1999; McHugh and Delanty, 2008; Benamer and Grosset, 2009; Hesdorffer et al., 2011; Kim et al., 2014), though there are some inconsistencies across studies due to a number of factors (Scharfman and MacLusky, 2014). When specific subtypes of epilepsy are selectively studied, there are more compelling gender differences (Christensen et al., 2005). For example, idiopathic generalized epilepsy is more common in women (McHugh and Delanty, 2008), as is a type of reflex epilepsy called photosensitive epilepsy (Taylor et al., 2007). Alternatively, focal cortical dysplasia is more common in males (Ortiz-Gonzalez et al., 2013), and males have a higher prevalence for a different type of malformation, perinodular heterotopia (Sisodiya et al., 1999).

A detailed review discussing the gender differences in temporal lobe epilepsy (TLE) has been published recently (Koppel and Harden, 2014). TLE is characterized by a progressive expansion of spontaneous seizures stemming from the limbic system regions, especially the hippocampus, and is often drug resistant. In essence, several aspects of TLE appear to differ in men and women. These aspects include auras, which are more common in females (Janszky et al., 2004), as well as differences in lateralization and generalization of seizures (Janszky et al., 2004). Voxel based morphometry shows abnormalities in men with TLE that are frontal, whereas, in women they are often more temporal (Santana et al., 2014). Reduced metabolism within the extratemporal region has been found to be more common in men than women with TLE (Savic and Engel, 1998; Nickel et al., 2003). Male preference is also reported in special epilepsy syndromes like Landau–Kleffner syndrome, epilepsy with continuous spike and wave complexes in slow wave sleep, epilepsy with myoclonic absences, West or Dravet syndromes, and benign epilepsy with centrotemporal spikes (Panayiotopoulos, 2007). Conversely, female preponderance was reported in juvenile myoclonic epilepsy (Camfield and Camfield, 2009; Janz, 1998), childhood absence epilepsy, perioral myoclonic with absences, and myoclonic encephalopathy in non-progressive disorders (Panayiotopoulos, 2007; van Luijtelaar et al., 2014).

Seizures do not occur randomly and tend to cluster in the majority of men and women with epilepsy; however, there are some sex-specific forms of epilepsy. Many of these are based on conditions that are mostly genetically-determined or based on natural fluctuations in hormonal status. Given the recent advances in genetic technology and genetic testing, epileptologists are now able to diagnose such patients more easily. However, there are many questions about the diagnosis and management of these genetic epilepsies, such as: When should these diagnoses be thought of? How are the seizures in these conditions? What other neurological, psychiatric and systemic problems are associated? What is the best treatment? These issues related to genetically determined epilepsies in both men and women will be addressed in future research.

There is little information on the clinical characteristics of genetically determined epilepsy that only affects women. PCDH19 is a serious and rare epileptic syndrome that affects only pediatric female patients—approximately 15,000–30,000 females in the United States (Tan et al., 2015; Ikeda et al., 2016). The condition, which is caused by an inherited mutation of the protocadherin 19 (PCDH19) gene, located on the X chromosome, is characterized by early-onset cluster seizures, cognitive and sensory impairment of varying degrees, and behavioral disturbances. The PCDH19 gene encodes a protein, protocadherin 19, which is part of a family of molecules supporting the communication between cells in the central nervous system. In case of mutation, protocadherin 19 may be malformed, reduced in its functionality or not produced at all. The abnormal expression of protocadherin 19 is associated with the occurrence of seizures beginning in the early years of life, mostly consistent of focal clustered seizures that last from one day to weeks. Often, but not always, the syndrome is also associated with a cognitive impairment of varying nature, and behavioral or social disorders with autistic traits. Currently, there are no approved therapies for PCDH19 female pediatric epilepsy. Neurosteroids, such as the synthetic GABA-A receptor-modulating ganaxolone, are proposed as symptomatic treatments in female children with epilepsy caused by a mutation of the PCDH19 gene. This epilepsy is characterized by cluster seizures and behavioral disturbances in girls. It is thought that the uncontrolled seizures are linked to PCDH19 mutation and to low levels of allopregnanolone, a naturally occurring neurosteroid in the brain (Lotte et al., 2016).

Many women with epilepsy experience a type of refractory epilepsy known as catamenial epilepsy, when seizures exacerbate with the menstrual fluctuation of sex hormones (Reddy, 2016a). The periodicities may differ between women with ovulatory and anovulatory cycles. There is emerging information on the role of sex hormones in pathogenesis of seizure exacerbation in catamenial epilepsy and whether the response to treatment can be predicted. The neuroactive properties of reproductive steroids and the variation of their serum concentrations in relation to the phases of the menstrual cycle may be critical factors for the development of catamenial seizure exacerbation. There is also some evidence to suggest that the laterality and focality of epilepsy may be a factor in the level of susceptibility to these presumed hormonal influences. Three types of catamenial seizures have been identified: perimenstrual (C1), periovulatory (C2), and inadequate luteal-phase (C3) (Herzog et al., 1997). Perimenstrual catamenial epilepsy is the most common clinical type. In perimenstrual catamenial epilepsy (C1), women with epilepsy experience an increase in seizure activity before, during, or after the onset of menstruation (Reddy, 2009a). The diagnosis of ovulatory or anovulatory cycles is often made by estimating the midluteal phase progesterone levels. Progesterone levels lower than 5 ng/ml during days 20 through 22 of the cycle would certainly indicate an inadequate luteal phase.

It is essential to discuss the effects of antiepileptic drugs and seizures on female reproductive function from puberty to menopause, as well as open a conversation about the current knowledge of the complex interactions between seizures, sex hormones, brain physiology, and medications in order to implement meaningful treatment approaches for women with epilepsy. Catamenial epilepsy is a multifaceted condition attributed to numerous causes. Catamenial epilepsy is an acquired disorder and currently there is no clear evidence of genetic components (Herzog, 2009; Quigg et al., 2009). A variety of mechanisms including fluctuations in antiepileptic drug levels, changes in water and electrolyte balance, and physiological variation in ovarian hormone secretion have been proposed as causes for catamenial epilepsy (Reddy et al., 2001; Gilad et al., 2008; Reddy, 2013a, 2013b). Estradiol has been known to play a role in the exacerbation of seizures in women with epilepsy (Logothetis et al., 1959; Bäckström, 1976; Jacono and Robinson, 1987; Younus and Reddy, 2016). Plasma estradiol levels are found to increase during both the follicular and luteal phase of the normal menstrual cycle. Thus, an increase in the ratio of estrogen-to-progesterone levels during the perimenstrual period might at least partly contribute to the development of perimenstrual seizure exacerbation (Bonuccelli et al., 1989; Herzog, 1991b). Progesterone plays a key role in catamenial epilepsy. Progesterone has long been known to have antiseizure activity in a variety of animal models of epilepsy (Craig, 1966; Bäckström et al., 1984; Landgren et al., 1978; Reddy, 2009a). Progesterone also has antiepileptogenic actions. The antiseizure actions of progesterone are mostly mediated by its metabolic conversion into neurosteroids (Reddy, 2004a, 2004b, 2010; Reddy and Mohan, 2011; Reddy, 2011; Reddy and Ramanathan, 2012). Changes in progesterone levels have been directly correlated with catamenial seizures (Reddy et al., 2004; Tuveri et al., 2008; El-Khayat et al., 2008). An extrasynaptic molecular mechanism involving tonic inhibition is shown to play a critical role in catamenial seizures and drug sensitivity (Reddy, 2016a).