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Review

Interaction between sex and early-life stress: Influence on epileptogenesis and epilepsy comorbidities

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ABSTRACT

Epilepsy is a common brain disorder which is characterised by recurring seizures. In addition to suffering from the constant stress of living with this neurological condition, patients also frequently experience comorbid psychiatric and cognitive disorders which significantly impact their quality of life. There is growing appreciation that stress, in particular occurring in early life, can negatively impact brain development, creating an enduring vulnerability to develop epilepsy. This aligns with the solid connections between early life environments and the development of psychiatric conditions, promoting the possibility that adverse early life events could represent a common risk factor for the later development of both epilepsy and comorbid psychiatric disorders. The influence of sex has been little studied, but recent research points to potential important interactions, particularly with regard to effects mediated by HPA axis programming. Understanding these interactions, and the underlying molecular mechanisms, will provide important new insights into the causation of both epilepsy and of psychiatric disorders, and potentially open up novel avenues for treatment.

Contents

Introduction

The epilepsies are a common group of neurological conditions affecting ~1% of the world's population at any one time. The defining clinical feature is the occurrence of spontaneous and recurrent epileptic seizures. Epileptogenesis, or the development of epilepsy, is underwritten by a series of biological processes which can be initiated by a variety of factors or combination of factors, including genetic abnormalities, brain injury, tumours, or febrile convulsions to name a few (Goldberg and Coulter, 2013; Pitkanen and Lukasiuk, 2011). Many of these occur early in life, impacting normal brain development. In addition, most, if not all, forms of epilepsy are associated with considerable cognitive and psychiatric comorbidity, which contribute greatly to disability and impaired quality of life (Hermann et al., 2008).

Emerging evidence points to an influence of early life environments as modulators of epileptogenesis (Koe et al., 2009), such that stressors in early life appear to accelerate epilepsy development. Indeed, early life febrile seizures are closely linked to the later development of temporal lobe epilepsy (Scantlebury and Heida, 2010). This complements the well-studied negative influence of adverse early environments on neurobehaviours which are commonly comorbid with epilepsy, such as cognitive dysfunction, and anxiety and depressive disorders

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(Hedges and Woon, 2011; Heim and Nemeroff, 2001). In addition, sex steroid hormones are recognised to influence seizure susceptibility and epileptogenesis (see other articles in this Issue), but whether sex-specific effects of early life stress on epileptogenesis exist is not clear. Given growing recognition of sex biases in several brain disorders, in particular some psychiatric disorders, it is timely to consider the influence of sex on the effect of early life stress on epilepsy. Understanding the role of gender in these diseases could have treatment implications for epilepsy and related psychiatric comorbidities, and also for delineating the causation of these disorders.

The purpose of this article is to review the evidence for sex differences with respect to the effects of early life stress and insults on epileptogenesis. An additional, yet no less important question is whether the prevalence or severity of psychiatric disorders, commonly comorbid with epilepsy, is also differentially impacted by sex. When considering this topic, several questions are raised; in particular, how to define 'stress', and what constitutes 'early life'? For the purposes of this review, we have taken the perspective that an early-life stressor may be any adverse incident or environmental challenge which occurs during pre- or post-natal life. Although maternal infection may adversely effect foetal development and increase the risk of epilepsy and behavioural disorders, we do not refer to, or include, infection as a stressor or other physical diseases as 'stressor' in this context. Since many of the pertinent studies are experimental, we limited the time frame to preweaning, but not for any scientific rationale, since brain development continues after this period. We will begin by reviewing experimental studies which document the influence of early life stress on epileptogenesis focussing on sex effects, and follow this with an account of sex differences in behavioural outcomes in the context of early life stress. Interactions between sex steroids and HPA axis programming and function could underlie any sex-specific effects on these outcomes. We conclude with a review of the clinical evidence which examines sex effects in this context. Future research directions are encouraged and suggested.

Sex-specific effects of early life stress on epileptogenesis

Several experimental studies have investigated the effects of different forms of early life stress on epileptogenesis and seizures (for recent reviews, see Ali et al., 2011; Huang, 2014; Koe et al., 2009; van Campen et al., 2013), with the predominant finding that early life challenges result in a vulnerability to the later development of epilepsy. There is also evidence that hyperthermia-induced prolonged seizures experienced in early life can result in the later development of epilepsy (Dube et al., 2010). A few of these studies have investigated the impact of sex, although the majority employ animals of only one gender. Table 1 lists the articles which have examined early life intervention influences on epilepsy outcomes, commenting on any observed sex effects.

The most striking study to investigate the interaction between early life stress and sex utilised a two-hit model of experiment temporal lobe epilepsy, combining early life (post-natal day 1 — p1) freeze-lesion induced cortical malformation with prolonged febrile seizures at p10 (Desgent et al., 2012). Video-EEG monitoring was used to detect the subsequent development of spontaneous seizures in the rats from p90–120. The authors found that, after the two 'hits', all male rats developed epilepsy, whereas none of the females did. While the histological damage induced by the cortical lesion was the same in both sexes, only males exhibited a rise in the stress hormone corticosterone as a consequence of the freeze injury. Intriguingly, a group of androgenised females which received testosterone treatment also experienced the corticosterone rise, and all developed epilepsy, suggesting that the hormonal response to the first hit may predispose, or predict, the influence of hyperthermic seizures on later epileptogenesis.

Amygdala kindling is a well-validated experimental model of epileptogenesis whereby repeated electrical stimulation of the amygdala results in the gradual development of seizure circuitry. Each stimulation elicits an electrographic and behavioural response, and as time progresses, the stimulations result in seizures which become increasingly longer and more convulsive as more brain regions are recruited into the seizure circuitry. This model has been widely used in epilepsy and epileptogenesis studies, and in drug development (Morimoto et al., 2004), and several papers have utilised kindling to investigate the effects of early life stress on the vulnerability to epileptogenesis. For example, Edwards and colleagues studied the effects of three episodes of restraint of the pregnant dam over three days in either early gestation or late gestation (Edwards et al., 2002), and compared the effects to offspring of non-stressed dams. In this study, male offspring of late gestational stress dams showed increased vulnerability to electrical kindling in adulthood compared to controls, but the stressed female rats showed no vulnerability to kindling, compared to non-stressed offspring. In another rat study incorporating kainic acid-induced seizures as the endpoint, pregnant dams exposed to 20 min of restraint stress on gestational day 18 had offspring which showed increased vulnerability to drug-induced seizures compared to offspring born to unstressed dams (Frye and Bayon, 1999). In this study, the effects of kainic acid appeared more pronounced in stressed male offspring than in the females.

Another study examined the influence of repeated restraint of pregnant dams at different gestational stages. Restraint stress during the later stages of gestation resulted in higher basal corticosterone levels in males (but not females) suggesting gender-specific aberrant HPA axis programming, and shorter latency to seizure following pilocarpine injection at p19. Pilocarpine also resulted in substantial mortality, with males experiencing late gestational stress being significantly more vulnerable than females.

In contrast to the above studies which identified increased vulnerability to epileptogenesis in males exposed to early life stress, Salzberg et al. (2007) reported that exposure to early life maternal separation stress resulted in a vulnerability to kindling epileptogenesis in early adulthood selectively in female rats, compared to early handled controls (Salzberg et al., 2007). This study also demonstrated that early life stress had an enduring effect to increase anxiety-like behaviours, but this behavioural consequence was not sex-specific. Subsequent studies demonstrated that female rats (but not males) exposed to this early life stress exhibited higher corticosterone surges as a consequence of the kindled seizures, and greater levels of neurogenesis, than early handled control rats (Kumar et al., 2011), suggesting potential mechanisms by which early life stress could mediate vulnerability to epileptogenesis. HPA axis programming, and elevated surges of corticosterone were also recently shown to be mechanistically involved in the ability of early life stress to increase the enduring vulnerability to kindling epileptogenesis in females (Koe et al., 2014). In this study, injection of the corticosterone synthesis inhibitor, metyrapone, prior to each kindled seizure abolished the corticosterone surge following seizures, and reversed the vulnerability induced by early life stress on epileptogenesis.

Although there are many to consider, a strong candidate mechanism to explain how sex might interact with early life stress, and stressors in general, to create vulnerability to epileptogenesis is via programming of the HPA axis. The HPA axis is the primary stress hormonal axis and, as discussed above, its function is distinctly plastic and modified by early life environments (Lupien et al., 2009). This axis is strongly implicated in the effects of early life stress on both epileptogenesis and behavioural disorders. In addition, the activity of the HPA axis can be modulated by the limbic system, notably the hippocampus and amygdala which are key structures involved in temporal lobe epilepsy. Several pieces of evidence support the claim that HPA axis responsivity may play a role in determining sex influences on the effects of early life stress on epilepsy vulnerability. First, the study by Desgent and colleagues showed that males, but not females, experienced epilepsy in their two hit model, and only males displayed a corticosterone response to the initial hit (Desgent et al., 2012). This indicates that sex-specific HPA axis