

Commentary on Li et al. “Disrupted female estrous cyclicity in the intrahippocampal kainic acid mouse model of temporal lobe epilepsy”

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Disruptions of biological rhythms represent an important category of epilepsy comorbidities. The dysfunctions of the biological clock occur on different levels, including circadian (eg, core temperature¹), infradian (eg, menstrual cycle²), and ultradian (eg, sleep structure³) domains. As other comorbidities, chronobiological dysregulation is likely to contribute to further deterioration of quality of life (QoL) in people in epilepsy. Yet, the problem has been receiving only scarce attention, especially in laboratory research.

Reproductive dysfunction is a common disorder in both women and in men with epilepsy.² For example, menstrual disorders are 2–3 times more prevalent in women in epilepsy than in the general population.⁴ Understandably, the negative impact of disruptions in the menstrual cycle may have profound detrimental effects on QoL, both psychological (eg, due to infertility), and biological (considering

ubiquitous role of sex hormones in regulating many essential physiological functions).

Understanding the mechanisms that underlie the disruptions of reproductive cycle is essential for their effective management. In turn, for mechanistic studies the availability of animal models of comorbidity between epilepsy and menstrual cycle disruption is critical. Indeed, only an animal system can afford the examination of biological basis of the comorbidity, by removing psychological factors and off-target effects of antiepileptic interventions. Earlier studies in adult male Sprague-Dawley rats using the self-sustaining limbic status epilepticus (SSLSE) model or hippocampal kindling, showed neuronal loss in certain hypothalamic regions (medial preoptic nucleus, dorsal medial hypothalamus) of rats with post-SSLSE epilepsy but not in kindled animals.⁵ Hypothalamic injury at the medial preoptic ventromedial, paraventricular, and ventral pre-mammillary

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nuclei was also demonstrated in adult male rats a few hours following systemic administration of pilocarpine or kainate to induce status epilepticus.⁶ Intrahippocampal kainic acid injection in adult female rats causes irregular estrus cycles during the latent phase (21–30 days postinduction) and lower progesterone levels.⁷ Similarly, disruption of the estrus cycle (increased diestrus and reduced proestrus in the third and fourth postpilocarpine weeks), sex hormone and gonadotropin levels, as well as reduced fertility were also reported in the pilocarpine rat model.⁸

Jiang Li and colleagues⁹ took an important step toward further validating an animal model of epilepsy-reproductive dysfunction comorbidity by analyzing the estrus cycle in mice (an equivalent of menstrual cycle in women), in which temporal lobe epilepsy (TLE) had been mimicked by intrahippocampal administration of kainic acid. The approach itself is commendable. Choosing mice as subjects opens opportunities for further genetic studies using respective knockout and transgenic approaches. The utilization of a widely employed model of TLE¹⁰ makes the findings commonly available to researchers. Furthermore, the paradigm itself is well suited to the purposes as it (1) involved local, rather than systemic administration of a convulsant agent, thus eliminating putative off-target effects associated with other models (eg, systemic pilocarpine), and (2) produced relatively infrequent recurrent seizures (≤ 3 per week), thus allowing focus on chronic comorbid state rather than postictal perturbations.

Through a detailed and meticulous analysis, the authors found that along with the emergence of spontaneous recurrent seizures, mice developed persistent disruption in estrus cycle, including the increased length and time spent in diestrus (nonfertile stage), and decreased time spent in estrus (fertile stage). The dysfunction occurred in the absence of gross ovarian pathology, thus pointing to the underlying neuroendocrine dysregulation along the hypothalamo-pituitary-gonadal axis. Of interest, 25% of the kainic acid injected mice still maintained regular estrus cycles. Given the important role of sex hormones on seizure susceptibility and epileptogenesis,¹¹ these data suggest that it may still be important to consider stratifying the animal studies using female rodents for epilepsy research according to the estrus cycle regularity to best dissect the interactions of neuroendocrine axis and epilepsy.

By virtue of its limited scope, the study did not pursue elucidation of concrete mechanisms underlying the estrus cycle disruption in the animals. Nevertheless, the quality of the core findings, and the absence of ovarian pathology, may help design prospective follow-up studies, such as detailed interrogation of hypothalamo-pituitary-gonadal axis (including the functioning of hypothalamic gonadotropin-releasing hormone [GnRH]-expressing, and of pituitary luteinizing hormone- and follicle-stimulating hormone-expressing cells, and the secretion of the respective hormones)²; the role of the laterality of epileptic

focus, which has been suggested for menstrual dysfunction in patients with epilepsy¹²; contribution of (even though infrequent) recurrent seizures, and of interictal epileptiform events (eg, spikes^{13,14} and high-frequency oscillations¹⁵). From the comorbidities perspective, an intriguing possibility is the connection between the estrus cycle disruption and epilepsy-associated depression. Indeed, on the one hand, serotonin exerts direct stimulatory effects on GnRH¹⁶; on the other hand, serotonergic dysfunction is a major driver of epilepsy-associated depression.¹⁷

In conclusion, the study by Li and colleagues represents an important step toward validating an animal system suitable for modeling and examining biological basis of reproductive dysfunctions in epilepsy. The follow-up studies outlined by the authors will certainly further enhance the importance of these findings. From a broader perspective, the study contributes to the field of chronobiological comorbidities of epilepsy. Congratulations!

Read the winning article “Disrupted female estrous cyclicity in the intrahippocampal kainic acid mouse model of temporal lobe epilepsy” online at <https://onlinelibrary.wiley.com/doi/abs/10.1002/epi4.12026>.

DISCLOSURE

The authors declare no conflicts of interest. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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