Female Hormones Prevent a Catastrophic Epilepsy in Male Mice

Neonatal Estradiol Stimulation Prevents Epilepsy in Arx Model of X-linked Infantile Spasms Syndrome.


Infantile spasms are a catastrophic form of pediatric epilepsy with inadequate treatment. In patients, mutation of ARX, a transcription factor selectively expressed in neuronal precursors and adult inhibitory interneurons, impairs cell migration and causes a major inherited subtype of the disease X-linked infantile spasms syndrome. Using an animal model, the Arx(GCG)10+7 mouse, we determined that brief estradiol (E2) administration during early postnatal development prevented spasms in infancy and seizures in adult mutants. E2 was ineffective when delivered after puberty or 30 days after birth. Early E2 treatment altered mRNA levels of three downstream targets of Arx (Shox2, Ebf3, and Lgi1) and restored depleted interneuron populations without increasing GABAergic synaptic density. Postnatal E2 treatment may induce lasting transcriptional changes that lead to enduring disease modification and could potentially serve as a therapy for inherited interneuronopathies.

Commentary

Infantile spasms (IS) is a catastrophic epilepsy syndrome occurring during the specific developmental period of infancy and early childhood. In addition to the stereotypic motor spasms, patients with IS typically develop long-term intellectual disability and other seizure types that are often resistant to treatment. A variety of acquired brain injuries at this critical age can result in IS, such as hypoxia–ischemia, meningitis, and traumatic brain injury. However, with advances in genetic testing, an increasing number of genetic mutations have been identified as etiologies of IS (1).

An X-linked recessive IS syndrome has recently been described in association with mutations in the Aristaless-related homeobox (ARX) gene (2). ARX mutations have also been implicated in causing a spectrum of related neurological disorders primarily affecting males, including X-linked lissencephaly with abnormal genitalia, Partington syndrome (intellectual disability with focal dystonia), and nonsyndromic mental retardation (3). The ARX protein is a transcriptional factor that modulates the expression of a number of other genes involved in migration and differentiation of interneurons. Thus, ARX mutations most likely cause IS due to migration defects of cortical and subcortical interneurons.

To investigate the pathophysiological mechanisms of ARX mutations in more detail, a number of mouse models have been created. A conventional knock-out mouse involving constitutive inactivation of the Arx gene in all cells dies shortly after birth but exhibits a small, malformed brain with a severe interneuron migration defect, confirming the critical involvement of ARX in cortical interneuron development (4). Another model, Arx(GCG)10+7 mice, incorporates the most common human ARX mutation causing X-linked IS syndrome, a triplet repeat polyalanine expansion in the ARX gene (5). This mouse model survives into adulthood and recapitulates a number of the phenotypic features of X-linked IS syndrome, including spasm-like seizures as pups and other severe seizures and cognitive impairment as adults. In addition, Arx(GCG)10+7 mice exhibit selective reduction of specific interneuron subtypes in cortex, hippocampus, and striatum.

This realistic ARX mouse model of X-linked IS syndrome provides the opportunity to identify downstream mechanisms involved in generating the phenotype and to assess rational, mechanistically targeted treatments for this disorder. Given the evidence of neuronal migration defects related to ARX mutations, one testable hypothesis involves hormonal regulation of cortical development. In particular, surges in estrogen—mediated by local conversion of testosterone in the male brain—and associated estrogen receptor expression during critical developmental stages have been implicated in promoting cortical development, including migration of interneurons (6, 7).

The recent study by Olivetti and colleagues tests whether estrogen administered during specific developmental periods modulates the phenotype of Arx(GCG)10+7 mice. Remarkably, they found that early estrogen treatment between the third and 10th postnatal days significantly reduces the motor spasms of male Arx(GCG)10+7 pups, and also decreases subsequent seizures in adult male mice. These behavioral effects of estrogen correlated with an increase in specific subtypes of
cortical interneurons, suggesting that estrogen may improve the epilepsy phenotype by correcting deficits in interneuron migration in Arx(GCG)10+7 mice. Furthermore, estrogen altered the expression of downstream genes normally targeted by ARX and implicated in cortical development. However, somewhat surprisingly, no detectable difference was found in GABAergic synaptic terminals, either in the mutant mice compared with controls or in the estrogen-treated mice. Thus, the specific downstream mechanisms directly causing and mediating the changes in the epilepsy phenotype are unknown. Importantly, late treatment with estrogen after 4 weeks of age had no effect on epilepsy in adult Arx(GCG)10+7 mice, indicating the developmental sensitivity of the early estrogen effect, possibly related to interneuron migration.

Regardless of the downstream mechanisms involved, the dramatic effects of early estrogen treatment in preventing later life epilepsy in Arx(GCG)10+7 mice appear consistent with a disease-modifying or antiepileptogenic effect—not simply seizure-suppression—and have important translational implications in considering novel clinical trials for patients with X-linked IS. However, the specificity and mechanistic relationship of estrogen’s action and X-linked IS are still ill-defined and, as a result, may actually have broader clinical implications. In particular, an underlying defect in estrogen metabolism or signaling in Arx(GCG)10+7 mice might account for estrogen’s beneficial effects from a mechanistic standpoint. However, no such abnormality in estrogen was identified in Arx(GCG)10+7 mice in this study. For example, a defect in conversion of testosterone to estrogen by the enzyme aromatase in the male brain might represent a rational explanation for impaired estrogenic regulation of cortical development and the corresponding corrective effects of estrogen, but brain expression of aromatase was normal in Arx(GCG)10+7 mice. Thus, it is not presently clear whether estrogen is correcting a specific mechanistic defect in Arx(GCG)10+7 mice or is simply compensating for another deficit.

Assuming there is no estrogen-specific defect in Arx(GCG)10+7 mice, the findings from this study suggest the possibility that estrogen could have broader applications for other neurological disorders involving impaired interneuron migration. From a therapeutic and translational standpoint, however, a critical issue is the timing of estrogen administration during development. In this study, the early estrogen treatment was started before the typical onset of spasms in Arx(GCG)10+7 mice. As later treatment starting in young adult mice was ineffective, the earliest feasible time to initiate treatment in patients would typically be at the first clinical presentation of spasms, but this was not tested in the mice. As much of early cortical development may be completed by this time, it remains to be seen whether estrogen treatment at the onset of spasms will maintain long-term disease-modifying effects.

Another clinically significant issue that was not addressed in this study is whether early estrogen treatment might also prevent the associated cognitive deficits that develop in IS, which are often more disabling than the seizures themselves. Arx(GCG)10+7 mice were previously documented to have associative learning deficits and autism-like abnormalities in social behavior (5), but the effects of estrogen on these neurobehavioral phenotypes were not reported in the current study. If estrogen is indeed found to improve cognitive and social outcomes, as well as having antiepileptogenic effects in Arx(GCG)10+7 mice, the clinical significance would be even more impressive. Nevertheless, while there are still a number of unanswered questions on the mechanistic and translational levels, this work provides reason for optimism for developing more effective treatments for catastrophic epilepsies of infancy.

by Michael Wong, MD, PhD

References

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