This Week in The Journal

Overexpressing Kainate Receptors Causes Autism-Like Behaviors

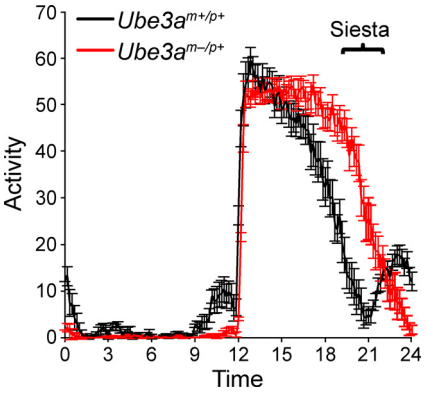
M. Isabel Aller, Valeria Pecoraro, Ana V. Paternain, Santiago Canals, and Juan Lerma

(see pages 13619–13628)

The complexly interwoven causes of autism spectrum disorder (ASD) are likely to be both genetic and environmental. Although the molecular players have yet to be identified, the process of setting up the brain's synapses has emerged as a critical factor in ASD, and genes that direct that process are now under investigation.

Genetic alterations can take many forms, including one called copy number variation, which leads to overproduction of the proteins encoded in a duplicated region of chromosome. In some ASD patients, copy number variation affects a gene called *GRIK4*, which encodes the GluK4 subunit of kainate-type glutamate receptors. Compared to AMPA- and NMDA-type glutamate receptors, the physiological role of kainate receptors remains poorly understood, but they have been shown to play a role in synapse development and circuit maturation in the cortex and hippocampus.

To determine the physiological effects of GluK4 overproduction in mice, Aller et al. created transgenic mice that overexpressed the receptor subunit under control of the promoter for calcium/calmodulin-dependent kinase II, which was limited to the neocortex, hippocampus, and striatum. In electrophysiological recordings from hippocampal CA3 synapses, spontaneous kainate receptor-mediated excitatory postsynaptic currents were larger and more frequent in the transgenic mice compared to wild type, suggesting that GluK4 receptors were more plentiful, resulting in augmented information transfer at these synapses. Remarkably, the mice displayed ethological behaviors indicative of ASD in humans, including disrupted social interactions and behaviors suggestive of depressive and anxious states. The findings suggest that dysregulation of Gluk4 expression might be a causative factor in ASD-related behaviors. Although more work will be required to understand the mechanism, the receptor might be the target of future therapies aimed at social and mood disturbances in ASD. The work also provides a new mouse model with which to study the brain circuitry affected by ASD.



Average daily wheel-running activity of Ube3a-deficient (red) mice, which do not break for a siesta like wild-type mice (black) do. See Ehlen et al. for details.

Angelman Syndrome Disrupts Sleep Homeostasis, Not Circadian Rhythm

J. Christopher Ehlen, Kelly A. Jones, Lennisha Pinckney, Cloe L. Gray, Susan Burette, et al.

(see pages 13587–13598)

Angelman syndrome, a genetic disorder characterized by intellectual disability, severely disrupts normal brain development, causing developmental delays and seizures and profoundly affecting speech, movement, and sleep. Patients sleep less and show disrupted sleep–wake cycles. Whether the disturbance arises from a defect in sleep homeostasis or in circadian control has remained an open question with therapeutic implications. Previous studies suggested circadian rhythm disturbances, but melatonin therapy has not solved sleep problems in Angelman's patients.

Angelman syndrome results from deletion or mutation of the maternal copy of the *UBE3A* gene, which encodes a ubiquitin ligase. Interestingly, the paternal allele of this gene is epigenetically silenced—so that it is not expressed—in all but a handful of neurons in mice as well as in people. Transgenic mice that lack the maternal allele ($Ube3a^{m-/p+}$) recapitulate the behavioral symptoms of Angelman syndrome and serve as a mouse model of the disorder.

Ehlen et al. set out to determine how loss of maternal *Ube3a* disrupts sleep in mice. When they placed $Ube3a^{m-/p+}$ mice in a 24 h dark cycle, the mice retained their normal circadian period; when researchers shifted the light–dark cycle, the mice were able to shift their sleep in response. Expression patterns of other circadian genes were normal in the transgenic mice. Together, the findings suggested that the circadian clock was intact in $Ube3a^{m-/p+}$ mice.

Ube3a loss might alternatively upset sleep homeostasis, which depends on the accumulation of so-called sleep pressure. The researchers next tracked the sleep and activity patterns in these mice. Wild-type mice became active at the start of a dark cycle for several hours, then took a remarkably consistent break, or siesta, for 2–3 h before resuming activity. $Ube3a^{m-/p+}$ mice also began the dark period with motor activity, but did not take a siesta, instead remaining active for much of the night. Total sleep time and daytime sleep patterns were similar in transgenic and wild-type mice, but the $Ube3a^{m-/p+}$ mice displayed less rapid eye movement sleep. A marker of sleep pressure called delta power increases over the course of the active period and declines during sleep. In $Ube3a^{m-/p+}$ mice, delta power increased much more slowly than in wild-type mice and did not increase in response to sleep deprivation, indicating that with the loss of Ube3a, sleep pressure failed to accumulate. The findings indicate that defective sleep homeostasis, not circadian control, is at the root of sleep disturbances in Angelman patients, which will hopefully lead to better therapeutic strategies.

This Week in The Journal is written by Stephani Sutherland, Ph.D.