THE HARTWELL FOUNDATION

2017 Individual Biomedical Research Award

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Remedying Sleep Disturbances in Autism Spectrum Disorder

Inadequate sleep in children may lead to hyperactivity, irritability, unstable emotions and impaired cognition; affecting day-to-day social interactions and academic achievement. Sleep is important for resetting the functional integrity of the brain and therefore, sleep disturbances in the vulnerable and developing brain of a young child can cause long term detrimental effects and adversely influence their cognitive development. Unfortunately, about 40-80% of children with autism spectrum disorder (ASD) suffer difficulty falling asleep, staying asleep, or in maintaining reasonable sleep duration. Such problems are positively correlated with the severity of ASD core symptoms, contribute to anxiety and complicate underlying social interactions, communication deficits and repetitive behaviors in affected children. While much is known about genetic and environmental factors thought to account for ASD, including the brain neural circuits responsible for controlling various behaviors, little is known about the underlying neural pathology associated with sleep disorder in ASD. In humans and other mammalian species, special neurons in a region of the brain kown as the preoptic area/anterior hypothalamus regulate sleep, but the underlying brain circuitry remains poorly understood. Thus it is not surprising that commonly available therapeutic interventions for ASD are rarely adequate to remedy concurrent sleep problems. To address this unmet need, Shinjae proposes to develop an effective therapeutic approach that will make it possible for a child with ASD to achieve good quality sleep, which she hypothesizes will alleviate the core symptoms of ASD. In order to uncover the changes in neural circuits that causally trigger sleep disturbances in ASD, she will use a mouse model of autism based upon DNA copy number variations in chromosome 16 deletions, which are known to profoundly increase the risk for ASD in children. Mice hemizygous for a 16p11.2 deletion have robust hyperactivity, wherein male mice, but not female mice, exhibit significantly more time awake and significantly less time in non-rapid-eye-movement sleep than their wildtype littermates. To understand how the activity of sleep neurons are altered during wakefulness and sleep, she will characterize the role of sleep neuron circuits within the hypothalamus of affected mice. She will also seek to identify the genes responsible for such sleep disturbances in the mouse by examining the effect of specific gene knock-outs using CRISPR-based genome editing and pharmacological manipulation. If Shinjae is successful in identifying the molecular and neural causes of sleep disturbances in ASD, translation of her research findings will make it possible to offer for the first time a therapeutic intervention for autism-related sleep disturbances, which will enhance the day-to-day functioning of affected children and their families and improve their quality of life.