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"Early-Life IL-6 Exposure Programs Hippocampal Synaptic Function and Spatial Cognition"

by

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Monday, March 16th, 2026
9:30 A.M.
Medical Science Building, B610

Join Zoom Meeting:
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Abstract

Autism (ASD) spectrum disorder is a neurodevelopmental disorder characterized by difficulties in communicating and interacting with other people. Successful social interaction requires acquiring information and reconstructing those memories to behave accordingly, highlighting the importance of the hippocampus. Case studies have established a strong association between infections and other environmental factors that cause inflammation with an increased risk for ASD. Epidemiologic studies have demonstrated that maternal infections stimulate the production of interleukin-6 (IL-6), which can cross the placenta and fetal blood-brain barrier to alter the normal development of the brain. This pattern of elevated IL-6 is maintained after birth in ASD children. In mice, inducing maternal immune activation at gestational day 12.5, changes neuronal development and that results in aberrant behaviors as adults, which can be prevented by neutralizing IL-6 in utero. Earlier studies evaluated the role of IL-6 using maternal immune activation mouse models that mimic infections in the first trimester of human gestation. However, epidemiological studies show that infections at the end of the second trimester pose the greatest risk for developing ASD. Thus, it is critical to understand how elevating IL-6 during the end of the second trimester affects brain development.

To model the effects of increased levels of IL-6 at the end of the second trimester of human development I injected male and female mice with either PBS, as a control, or with 75 ng IL-6 twice daily, from post-natal day 3 until post-natal day 6 a developmental mouse stage that matches weeks 24-30 of human gestation (the end of the second trimester and beginning of the 3rd trimester). Our published studies have shown that this IL-6 treatment paradigm altered patterns of ultrasonic vocalizations, reduced social interactions and increased self-grooming in male mice, displaying mouse versions of the three core symptoms of autism. Since many individuals with ASD have intellectual disabilities, the goal of this study was to evaluate performance on memory tests and to correlate their performance on the memory tests with hippocampal physiology.

Unexpectedly, in tests of cognitive function, the IL-6 treated male mice either performed better than the controls or their performance was not different. For example, when tested at 6 weeks of age in the novel object location test, the IL-6-treated males spent *more* time exploring an object at the new location compared to the controls, while the IL-6-treated females showed no preference for the new location. Similarly, in the T-maze, the IL-6 treated male mice tended to explore the novel arm more than the controls. In the paired associative learning task the IL-6-treated male mice learned and remembered the spatial location of three different visual stimuli at the same pace as the controls.

To directly evaluate hippocampal function, I induced long-term potentiation (LTP) in the CA1 region using hippocampal slices and found that the male mice showed a 15% increase in the acquisition of LTP. When Long-term depression (LTD) was induced, the male mice showed a larger depression of the field potential by 26 % vs. the controls. Female mice showed no significant changes in LTP or LTD. In addition, the input/output function of IL-6-injected male mice was decreased by 10% compared to control, but the paired pulse ratio was unchanged between the groups, indicating that the increased synaptic plasticity is caused by post-synaptic and not pre-synaptic changes.

IL-6 treatment also produced long lasting subcellular and molecular changes within the hippocampus. At 6 weeks of age, total apical dendritic spines were reduced by 34 % in the CA1 region of the IL-6-treated males, and there was a 69% increase in thin spines. Within synaptosomal preparations from the hippocampus, steady state levels of the glutamate receptor subunit GluA2 that was situated on the external plasma membrane was decreased in IL-6-treated mice compared to controls. The combined reduction in spine density and decreased available AMPA receptor levels on the postsynaptic membrane likely predisposed the IL-6-treated mice to enhanced LTD. Taken altogether, these data show that a short increase in circulating IL-6 is sufficient to cause lasting changes in hippocampal synaptic plasticity and function. Supported by NS116828-04 awarded to SWL.