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The Role of Microglia in the Sculpting of Developing Stress Circuits by Early-Life Adversity

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Background: Early-life adversity can have a profound and lifelong impact on an individual's risk for emotional disorders such as depression, likely by modulating the maturation of brain circuits. We find that early-life exposure to an impoverished environment and unpredictable maternal care (in a limited bedding and nesting [LBN] paradigm) provokes major alterations in cognitive and emotional function, including anhedonia, accompanied by aberrant connectivity between the hippocampal-limbic system and reward/pleasure-related regions. Within the hypothalamus, this early-life adversity causes an increase in the number of excitatory synapses onto corticotropin-releasing hormone (CRH)-expressing neurons in the paraventricular nucleus (PVN). Such synaptic changes suffice to induce large-scale and enduring epigenomic changes in the expression of neuronal genes, including Crh. However, the mechanisms by which early-life adversity modulates synapse development or persistence in developing brain circuits remain unknown. We hypothesize that microglia contribute to normal synapse reduction on CRH neurons in the developing PVN, and that adverse early-life experiences interfere with this function.

Methods: To interrogate microglial function, we employed male and female dual-reporter transgenic mice with visible CRH neurons and microglia and two-photon time-lapse imaging in acute slices of the PVN. We obtained these hypothalamic slices from P8 mice that were reared in LBN or control cages from P2 to P8. We then visualized live microglial process dynamics and their interactions with CRH neurons. In fixed tissue, we utilized 3D-reconstruction confocal microscopy and immuno-detection of pre- and post-synaptic markers to quantify in high-resolution the developmental trajectory of synapse density and engulfment by microglia in the PVN. To probe whether microglial function is required for normal synapse development, we inhibited microglial function with minocycline or a specific Mer inhibitor and assessed synapse number on CRH neurons. In a final mechanistic experiment, we capitalized on cell type-specific DREADD technology to express activating Gq-DREADDs in microglia and delivered CNO continuously via a subcutaneous slow-release pellet from P3 to P10. We then probed whether this exogenous activation of microglia prevented the effects of early-life adversity on microglial function and synapse number on CRH neurons.

Results: Early-life adversity augmented the number of vGlut2+/PSD95+ excitatory synapses onto CRH neurons by the end of the LBN experience (P10) in both males and females, without altering the number of CRH neurons or microglia in the PVN at P4, P8, or P10. However, microglial processes overlapped more substantially with CRH neurons at P8 than P4, potentially indicating a period of greater microglial-neuronal interaction. Pharmacological inhibition of microglia increased the density of excitatory synapses onto CRH+ neurons, phenocopying early-life adversity, and supporting the idea that microglia regulate synapse number in the developing PVN. Live-imaging revealed that microglial process dynamics were diminished in the PVN of P8 LBN mice, concomitant with decreased microglial engulfment of vGlut2+ presynaptic terminals. Characterization of whether DREADD-mediated microglial re-activation can prevent the adversity-induced microglial dysfunction and synapse excess onto CRH neurons is currently ongoing.

Conclusions: Microglia are potential contributors to early-life experience-dependent sculpting of stress-sensitive circuits. Ongoing studies include manipulation of microglial function during development aiming to prevent stress-related emotional disorders in adulthood, thereby providing novel targets for therapeutics or preventative interventions.

Keywords: Microglia, Synapse Growth-Pruning, Early-Life Adversity, Corticotropin-Releasing Hormone, Paraventricular Nucleus of the Hypothalamus

Disclosure: Nothing to disclose.