Title
Patterned Sensory Signals During Sensitive Periods Enable Brain Circuit Maturation: Synapses, Microglia, Behaviors

Journal
NEUROPSYCHOPHARMACOLOGY, 46(SUPPL 1)

ISSN
0893-133X

Author
Baram, Tallie Z

Publication Date
2021

Peer reviewed

PANEL

54. Impact of Unpredictable Parental and Environmental Signals on Neural Circuit Maturation and Mental Health

54.1 Patterned Sensory Signals During Sensitive Periods Enable Brain Circuit Maturation: Synapses, Microglia, Behaviors

Tallie Z. Baram

University of California- Irvine, Irvine, California, United States

Background: Brain circuits, comprised of neuronal ensembles communicating via synapses, execute complex behaviors involved in mental health and disease. During sensitive developmental periods, activity, largely in response to sensory signals, governs which synapses are strengthened or pruned, and this selective sculpting enables circuit maturation. We have identified reduction of excitatory synapses onto stress-sensitive hypothalamic neurons after predictable barrages of sensory stimuli to neonatal rats, and, in contrast, enduring exuberant excitatory innervation of the same cells after exposure to unpredictable chaotic sensory input. We further demonstrated that these changes in excitatory synapse density on CRH-expressing neurons in the paraventricular hypothalamic nucleus are important, as they promote muted or protracted responses to stress throughout life.

Methods: To probe the mechanisms by which excitatory synapse density is augmented by unpredictable patterns of sensory input (FRAG) early in life, employ multiple methodologies in vivo and in vitro centered on the role of microglia. Employing a suite of transgenic mice we used live two-photon imaging to determine microglial process dynamics, selective chemogenetic manipulation of microglia, confocal and electron microscopy and hormonal and behavioral assays in both sexes.

Results: We identified disrupted synapse pruning by microglia as a mechanism for aberrant sculpting of the innervation to stress-sensitive neurons. Microglial process dynamics, assessed using 2-photon microscopy ((t16 = 2.79, $p = 0.01$), and engulfment of synaptic elements by microglia ((t13.87 = 2.22, $p = 0.04$), were attenuated in FRAG mice versus controls, related to deficient signaling of the microglial phagocytic receptor MerTK. Accordingly, selective chemogenetic activation of FRAG mouse microglia rescued microglial process dynamics and reduced excitatory synapses density to control levels. Notably, such early-life microglial activation ameliorated the augmented and prolonged stress responses in adult FRAG mice.

Conclusions: Together, the data indicate that unpredictable patterns of sensory inputs prevent selective pruning of synapses, perhaps via absence of selective Hebbian plasticity. They establish microglial actions during development as powerful contributors to the enduring, experience-dependent sculpting of stress-related brain circuits, which, in turn, governs life-long behaviors.

Disclosure: Nothing to disclose.