

UNIVERSITY OF RHODE ISLAND
Department of Chemistry
SEMINAR

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***“Dysregulation of neural activity and
microglia function following exposure to
the global environmental contaminant
perfluorooctane sulfonate (PFOS)”***

HOST
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Dysregulation of neural activity and microglia function following exposure to the global environmental contaminant perfluorooctane sulfonate (PFOS)

Per- and Polyfluoroalkyl Substances (PFAS) are a class of highly persistent global contaminants that, due to their structural stability, have been termed “forever chemicals”. A subset of PFAS congeners have been deemed immune hazards as result of their immunotoxic effects on cellular components of the adaptive immune system; however, comparatively little is known about how PFAS exposure effects the development and functioning of the innate immune system. Given the critical role of innate immune cells, namely microglia, in the brain development and homeostasis, we used larval zebrafish brain injury model to examine whether developmental exposure to a prevalent PFAS congener, perfluorooctane sulfonate (PFOS), disrupts microglia function. Embryonic PFOS exposure induced an activated microglia phenotype, which led to a significant increase in microglial recruitment to a site of brain injury and prolonged microglial presence at and beyond the injury site. Microglia activation and recruitment was not concurrent with increased cell death or inflammation, but was accompanied by an upregulation of *p2ry12*, a G-coupled protein receptor that is involved in microglial activation and migration. Microglia behavior could be normalized in PFOS-exposed larvae by using optogenetics to hyperpolarize microglia and drive them towards a homeostatic state. As PFOS exposure has been shown to cause behavioral hyperactivity, we asked whether heightened neuronal signaling was modulating the observed microglial responses in PFOS-exposed larvae. Indeed, PFOS exposure led to an increase in neuronal calcium firing at a range of PFOS concentrations. Recapitulating neuronal hyperactivity via exposure to the GABAA receptor agonist pentylentetrazol was sufficient to induce microglia hyper-responsiveness to injury, while neuronal silencing via optogenetics was able to normalize the microglial responses in PFOS exposed larvae. Lastly, exposure to perfluorooctanoic acid (PFOA), an immunotoxic 8-carbon PFAS with a carboxylic functional group, did not elevate neuronal activity or produce an exacerbated microglial response to injury. This study reveals that developmental exposure to an environmental contaminant can alter neural activity and prime the reactivity of microglia to injury, and provides a novel view of how structurally similar PFAS congeners can differentially impact the CNS.