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MASTER THESIS PROJECT

Using gene editing to understand how exposure to Per- and Polyfluoroalkyl Substances (PFAS) cause Developmental Neurotoxicity (DNT)

Submitted by

IFEOLUWA EHIMARE OMOYENI

Helmholtz Centre for Environmental Research – UFZ

Leipzig, Germany.

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Universidad del Pais Vasco Euskal Herriko Unibertsitatea
université de BORDEAUX
UNIVERSITÉ DE PAU ET DES PAYS DE L'ADOUR
LIÈGE université
NTNU Norwegian University of Science and Technology
U.PORTO

SUMMARY

Neurodevelopmental disorders are an increasing public health concern, in part due to xenobiotic exposure-dependent developmental neurotoxicity (DNT). Per- and polyfluoroalkyl substances (PFAS) are a diverse class of chemicals used in over 200 industrial and consumer applications. Perhaps unsurprisingly, they are ubiquitously found in the environment. Previous work suggests that alkyl sulfonic acid PFAS represent one particularly problematic PFAS sub-class that might specifically cause DNT, characterized by a hyperactivity phenotype in larval zebrafish. However, there is a gap in our understanding of the mechanisms governing hyperactivity caused by exposure to alkyl sulfonic acid PFAS. To better characterize the effects of alkyl sulfonic acid PFAS exposure on behavioural endpoints, we assessed the acute neurotoxicity of PFOS or PFHxS and determined whether hyperactivity in PFOS- or PFHxS-exposed larvae persist following compound removal. Finally, to potentially reveal underlying mechanisms governing PFAS-dependent hyperactivity, we investigated whether ppard mediates PFOS- or PFHxS-dependent hyperactivity using CRISPR/Cas9 gene editing. The hyperactivity phenotype were demonstrated using visual startle response (VSR) and light/dark transition locomotor response (LMR) behaviour tests. In the LMR test, acute exposure to 2.47-7.86 μM PFOS caused increased swimming activity in the dark period 60 min post-exposure but failed to provoke VSR hyperactivity. In contrast, PFHxS acute exposure caused dark phase hyperactivity 340 min and 410 min post-exposure. Similar to PFOS, acute exposure to PFHxS also failed to trigger VSR hyperactivity. To test the hypothesis that the hyperactivity phenotype arises from a developmental perturbation, a chemical washout experiment was performed. For both chemical compounds, concentration-dependent dark phase hyperactivity was transient, yet VSR hyperactivity was persistent and irreversible. Finally, we determined that knockdown of ppard was not sufficient to block PFAS-dependent dark phase or VSR hyperactivity. Taken together, this work shows for the first time that alkyl sulfonic acid PFAS cause acute and reversible dark phase hyperactivity, suggesting a toxicokinetic mechanism. In the case of VSR hyperactivity, we report that this phenotype likely arises from a developmental perturbation as it is persistent and irreversible.