Rearing environment modulates the phenotype of genetically homogeneous mice: a multi-center study

Jaric I (1), Voelkl B (1), Clerc M (2,3), Schmid M (4), Novak J (1), Rosso M (1), Rufener R (5), von Kortzfleisch VT (6), Richter H (6), Buettner M (7), Bleich A (7), Amrein I (8,9), Wolfer DP (8,9), Touma C (10), Sunagawa S (2,3), Würbel H (1)

(1) University of Bern, Vetsuisse Faculty, Animal Welfare Division, Bern, Switzerland
(2) ETH Zürich, D-BIOL, Institute of Microbiology, Zürich, Switzerland
(3) Swiss Institute of Bioinformatics, Zürich, Switzerland
(4) MWSchmid, GmbH, Glarus, Switzerland
(5) Karolinska Institutet, Department of Oncology-Pathology, Solna, Sweden
(6) University of Münster, Department of Behavioural Biology, Münster, Germany
(7) Hannover Medical School, Institute for Laboratory Animal Science, Hannover, Germany
(8) Institute of Anatomy, University of Zurich, Switzerland
(9) Institute for Human Movement Sciences and Sport, ETH Zurich, Switzerland
(10) University of Osnabrück, Behavioural Biology, Osnabrück, Germany

Aim: To investigate possible causes of poor replicability in behavioral neuroscience research, we determined the extent to which common differences in housing and husbandry conditions between rearing facilities (RFs) contribute to the replicability problem by modulating the phenotype of genetically homogenous (inbreed) mice. Methods: We reared inbred C57BL/6JRj mice from a single breeding stock in five different RFs throughout early life and adolescence, before transporting them to a single test laboratory. We examined the extent and persistence of variation in the composition of the gut microbiota associated with the different RFs and measured differences in behavioral and physiological phenotypic traits. We also assessed chromatin accessibility in the ventral hippocampus to explore the biological basis of behavioral differences. Results: We found persistent effects of RFs on the composition and heterogeneity of the gut microbiota. These effects were paralleled by persistent differences in body weight and behavior. We show that the facility-specific environment influenced developmental programs by affecting neuronal chromatin accessibility profiles, likely modulating the mice' behavioral phenotypes. We detected changes in chromatin organization of genes involved in the regulation of behavior, neurogenesis and presynaptic plasticity events, targeting mainly GABAergic and glutamatergic transmission. Conclusion: Our findings demonstrate that common environmental differences between RFs may produce facility-specific phenotypes, from the molecular to the behavioral level, which might explain inconsistency of results between different studies. The results highlight that the animals' environmental background should be accounted for by study design to produce robust and replicable research findings.