【Grant-in-Aid for Scientific Research(S)】

Integrated Science and Innovative Science (New multidisciplinary fields)

Title of Project： Elucidation of developmental neurotoxicity mechanisms microstructural analysis

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Research Area：Risk sciences of radiation/chemicals
Keyword：Hazardous chemicals, Environmental toxicology, Social medicine

【Purpose and Background of the Research】

Accumulating evidence of biomedical sciences supports the Barker's hypothesis, 'Developmental origins of adult disease', proposing that undernutrition during the fetal period enhances the incidence of adult disease later in life. In addition to the nutritional deficiency, environmental factors, such as environmental chemicals, during gestation have been suggested to affect health states of children. In particular, the higher brain functions are suspected to be vulnerable to much lower dosage of chemicals than other toxicity endpoints (referred as developmental neurotoxicity, hereafter). Nevertheless, animal data on the developmental neurotoxicity has been seldom adopted to derive tolerable intake values. The possible reasons are the scarcity in reproducibility of behavioral test results and the difficulty in characterizing animal behaviors. Thus, we have developed new behavioral tests and found that exposure to low doses of dioxin (TCDD) and bisphenol A (BPA) induces abnormality in the higher brain function (learning, perseverance etc.). In this study, we plan to elucidate the toxicity mechanism of environmental chemicals at the developmental stage by focusing on microstructural alterations of the brain.

【Research Methods】

Animals exposed to chemicals will be prepared according to the previous studies and our own experience, and the dose of chemicals is chosen on the one that does not harm dams and pups by gross observations. As test chemicals, 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin and bisphenol A will be used. Behavior of the animals will be examined when necessary.

Using transgenic mice harboring a fluorescent probe, we will intensively study how TCDD or BPA exposure will alter the microstructure of the brain, by the developmental trend analysis.

Next, we will analyze gene expressions of the developing brains of mice exposed to chemicals during fetal and lactational period, and mine genes with significantly altered expressions (such as receptor genes, their related genes, and their downstream genes. We also plan to perform microarray analysis for the particular period and brain region.

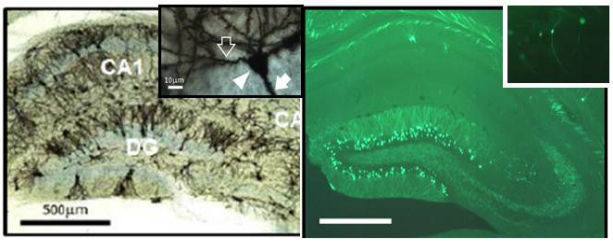

Figure 1. An example of the microstructural analysis of the mouse hippocampus

【Expected Research Achievements and Scientific Significance】

By setting the low-dose chemical effects in laboratory animals as start point, the tackle to elucidate the toxicity mechanism is the unique feature of this study in itself, and is useful for the risk assessment. The achievement of this study is anticipated to contribute to the advancement of toxicology/neuroscience as well as regulatory science.

【Publications Relevant to the Project】

1. Yoshioka W, Peterson RE, Tohyama C. Molecular targets that link dioxin exposure to toxicity phenotypes. J Steroid Biochem Mol Biol. 127:96-101, 2011.
2. Tse D, Takeuchi T, Kakeyama M, Kajii Y, Okuno H, Tohyama C, Bito H, Morris RG. Schema-Dependent Gene Activation and Memory Encoding in Neocortex. Science. 333:891-895, 2011.

【Term of Project】FY2012-2016

【Budget Allocation】166,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://env-health.m.u-tokyo.ac.jp/