

Title of Research:

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Establishment of an adverse outcome pathway for the evaluation of developmental neurotoxicity in chemical-induced hypothyroidism

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Summary of Research:

Recently, the concern over environmental chemicals that induce hypothyroidism has been increased, since hypothyroidism in pregnancy can have a significant impact on the development of the fetal brain in human. However, detection of abnormalities in thyroid function of pregnant animals in developmental toxicity tests have not been sufficiently utilized for risk assessment of chemical substances because the detailed causal relationship between the thyroid function abnormalities and adverse effects on the development of the fetal brain remains unclear. In order to solve such a problem, we focused on differentiation markers of mature neurons and produced reporter transgenic mice (Tg mice) carrying luciferase (Luc2) and LacZ genes downstream of a neuronal differentiation marker promoter. In this fiscal year, we characterized the expression profile of *in vivo* imaging in the brain during the developmental stage of Tg mice and analyzed the expression profile when hypothyroidism was induced in pregnancy. The daily profiles of *in vivo* imaging in the brain of Tg pups consisted with those of *in vitro* reporter assay in the removed brain. In addition, when antithyroid drugs are administered to pregnant Tg mice under conditions that induce hypothyroidism, *in vivo* imaging was possible to capture their effects on the brain of Tg pups. These results suggest that *in vivo* imaging with our Tg mice may be able to noninvasively detect the effects of chemical exposure during pregnancy on the brain development in pups. In the next fiscal year, the effects of hypothyroidism during pregnancy on the brain development in pups will be examined in detail using the expression profile of reporter gene.

Timeline: April, 2021 – March, 2022

Topics:

None

Conference Presentations:

- 1) Ishida K, Minamigawa Y, Mori K, Matsumaru D, Nakanishi T, Characterization of neuronal differentiation tracer mouse for novel developmental neurotoxicity evaluation system, The 48th Annual Meeting of the Japanese Society of Toxicology (Kobe), 2021.
- 2) Minamigawa Y, Ishida K, Mori K, Tatsumi K, Matsumaru D, Takuma K, Nakanishi T, Validation of neuronal differentiation tracer mice for a novel developmental neurotoxicity *in vivo* evaluation system, Forum 2021 Pharmaceutical Health Sciences/Environmental Toxicology (Chiba), 2021.



Development and assessment of new risk assessment methods