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

Integrated Science and Innovative Science (New multidisciplinary fields)

Title of Project : Molecular mechanisms underlying the imprinting of sexual immaturity and failure of maternal nursing caused by environmental pollutants

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Research Area : Pharmaceutical and Environmental Health Sciences
Keyword : Dioxin, Sexual Immaturity, Nursing Defect, Imprinting, Pituitary Hormone

【Purpose and Background of the Research】

It is suspected that environmental pollutants harm species conservation and the health of future generations. In this context, many epidemiological studies including Japanese ones (http:// www.env.go.jp/chemi/ceh/) are now being undertaken focusing on the relationship between child growth and environmental chemicals.

This laboratory has been involved in clarifying the effects of dioxin, a prototype of environmental pollutants, on future generations and its mechanism of action using a rat model. The data we have obtained to date demonstrate that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a very toxic dioxin, imprints sexual immaturity at adulthood by reducing sex-steroids in the fetal/infant stages via initial damage to pituitary luteinizing hormone (LH)(Fig. 1). In addition, TCDD retards the growth of infants and nursing activity of their dams probably due to a reduction in growth hormone (GH) and prolactin (PRL), respectively (Fig. 1). This project aims to investigate the mechanisms whereby TCDD reduces pituitary hormones, and to develop a strategy to overcome TCDD damage to fetuses/infants.

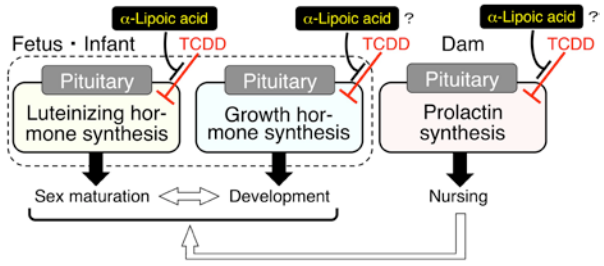

Figure 1. Proposed mechanism for TCDD-produced sexual immaturity and its restoration by LA

【Research Methods】

1) The results of our recent study have suggested that TCDD reduces LH production by inducing histone deacetylases (HDACs) and, so, the mechanism of HDAC induction has been clarified. 2) TCDD also reduces the fetal hypothalamic content of α-lipoic acid (LA). LA supplementation restored a TCDD-produced reduction in fetal LH (Fig. 1). Because LA is an endogenous substance necessary for ATP production, the role of the damage to ATP synthesis in an LH reduction and its mechanism are being investigated. 3) The reason why the perinatal damage to LH is linked to sexual immaturity is being clarified. 4) The relevance of attenuated GH/PRL levels to infant growth and maternal nursing together with mechanisms for hormone reduction are also being investigated. 5) In addition to TCDD, the effects of other pollutants such as methylmercury on the pituitary-gonad axis are also being studied.

【Expected Research Achievements and Scientific Significance】

This project will clarify the reason why dioxin and other endocrine disruptors are hazardous to reproduction and development. Based on the protective effect of LA, a cellular component, the development of dietary strategies to eliminate the harmful effects of dioxin would be very useful.

【Publications Relevant to the Project】

1. Koga, T., Ishida, T., Takeda, T., Ishii, Y., Uchi, H., Tsukimori, K., Yamamoto, M., Himeno, M., Furue, M., Yamada, H., Restoration of dioxin-induced damage to fetal steroidogenesis and gonadotropin formation by maternal co-treatment with α-lipoic acid. ***PLoS ONE***, 7, e40322 (2012).
2. Takeda, T., Fujii, M., Taura, J., Ishii, Y., Yamada, H., Dioxin silences gonadotropin expression in perinatal pups by inducing histone deacetylases: a new insight into the mechanism for the imprinting of sexual immaturity by dioxin. ***J. Biol. Chem.***, 287, 18440-18450 (2012).

【Term of Project】 FY2012-2016

【Budget Allocation】 151,100 Thousand Yen

【Homepage Address and Other Contact Information】

http:// http://eisei.phar.kyushu-u.ac.jp/