【Grant-in-Aid for Scientific Research(S)】
Integrated Science and Innovative Science (New multidisciplinary fields)

Title of Project : Signal toxicity mediated through nuclear receptors of new generation bisphenols

Yasuyuki Shimohigashi
(Kyushu University, Faculty of Sciences, Professor)

Research Area : New multidisciplinary fields

Keyword : Endocrine disruptors, Bisphenols, Nuclear receptors, Signal toxicity

【Purpose and Background of the Research】

Our discovery of the specific receptor of endocrine disruptor bisphenol A (BPA), namely, estrogen-related receptor γ (ERRγ), has impacted the studies on BPA's low-dose effects. Meanwhile, novel polycarbonate plastics made from new generation bisphenols (AF, B, C2, E, and Z as replacement of BPA) have been newly developed, and their possible and potential endocrine disruptions are now worried greatly.

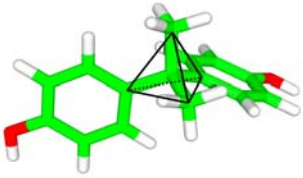

Fig. 1. Bisphenol A in the most stable conformation.

Because of high ERRγ expression in the fetal brain, BPA is likely concerned with adverse effects on development and differentiation of the central nervous system. We recently found the feedback system in which ERRγ regulates a number of nuclear receptors and transcription factors. The present objectives are to clarify the molecular mechanisms of signal toxicity mediated through nuclear receptors of diverse bisphenols.

【Research Methods】

The investigation of molecular machinery of the fetal brain is to shed light on the influence of BPA and other bisphenols in the central nerve system. Those include the identification of ERRγ's target genes by ChiP, real-time PCR analysis of gene expression in BPA-feeding animals, the structural and cellular analyses of signal toxicity mediated by nuclear receptors, and many other intrinsic experimentations.

【Expected Research Achievements and Scientific Significance】

A special concern is signal toxicity in the cranial nerve. High expectation is due to the establishment of the molecular basis of intrinsic risk assessment of bisphenols.

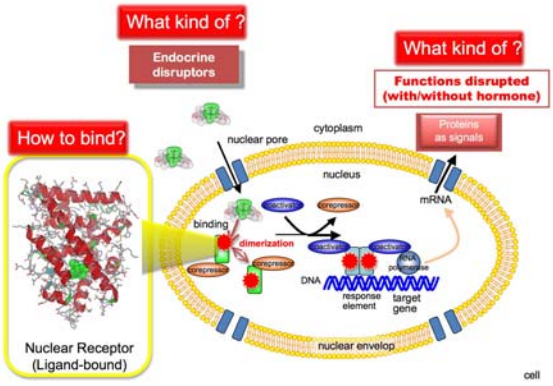

Fig. 2. Schematic diagram of signal toxicity mediated through nuclear receptors of new generation bisphenols.

【Publications Relevant to the Project】

A. Matsushima, X. Liu, H. Okada, M. Shimohigashi, and Y. Shimohigashi: Bisphenol AF is a Full Agonist for the Estrogen Receptor ERα, but a Highly Specific Antagonist for ERβ. *Environ. Health Perspect.*, in press. Online 28 4 2010 | doi:10.1289/ehp.0901819

A. Matsushima, Y. Kakuta, T. Teramoto, T. Koshiba, X. Liu, H. Okada, T. Tokunaga, S. Kawabata, M. Kimura, and Y. Shimohigashi: Structural Evidence for Endocrine Disruptor Bisphenol A Binding to Human Nuclear Receptor ERRγ. *J. Biochem.*, **142(4)**, 517-524 (2007).

【Term of Project】 FY2010-2014

【Budget Allocation】 120, 600 Thousand Yen

【Homepage Address and Other Contact Information】

http://lsfb.scc.kyushu-u.ac.jp/
E-mail: shimo@chem.kyushu-univ.jp