Effects of 1,3,7-tribromodibenzo-*p*-dioxin, a natural dioxin on chicken embryos: comparison with effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

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Aim and procedure

1,3,7-Tribromodibenzo-p-dioxin (1,3,7-TriBDD) is a dominant congener among naturally occurring PBDDs throughout the marine food web. Concentrations of 1,3,7-TriBDD ranging from 0.002 pg/g to 160 ng/g were detected in marine algae, sponges, shellfish, and fish. Mussels accumulate 1,3,7-TriBDD by ingesting various algal species and are prey resources for marine birds. Thus, naturally occurring 1,3,7-TriBDD may potentially affect higher trophic animals, including different avian species that prey on mussels exposed to 1,3,7-TriBDD. In addition, a previous study pointed out the possibility of increasing concentrations of 1,3,7-TriBDD in the marine environment, as climate change may increase the populations of algal species producing 1,3,7-TriBDD. Despite the potentially growing risk of 1,3,7-TriBDD to the marine ecosystem, the effects of 1,3,7-TriBDD on animals, including avian species, have not fully been investigated.

Therefore, this study aimed to investigate the effects of 1,3,7-TriBDD exposure on chicken embryos, which is a sensitive avian model to dioxin exposure. A transcriptomic analysis of the liver of chicken embryos treated with 1,3,7-TriBDD was performed. Moreover, a bioinformatic analysis of differentially expressed genes (DEGs) induced or repressed by 1,3,7-TriBDD exposure was performed to provide insights into the effects of this congener on DEG-enriched pathways. A similar experiment was performed with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a representative and the most toxic compound among dioxins, and the results were compared with those of 1,3,7-TriBDD.

Results

Transcriptome analysis revealed that genes with expression levels altered by exposure to 1,3,7-TriBDD were primarily categorized in cancer- and metabolism-related pathways. These results suggest that 1,3,7-TriBDD possibly induces cancer and metabolic alterations. The transcriptome analysis of the chicken embryos treated with 2.5 μM TCDD

(T2.5/Control) identified similar representative pathways as 1,3,7-TriBDD administration.

Within the cancer-related pathways, the overall transcriptomes of the groups treated with 1,3,7-TriBDD and TCDD tended to be upregulated. Pathways in the KEGG database most relevant to hepatocellular carcinoma included the MAPK signaling pathway, oxidative stress, TGFβ signaling pathway, and Pi3-Akt signaling pathway. The activation of these pathways desensitizes tumor cells to antigrowth signals by preventing exclusion and apoptosis, and dysregulating cell proliferation. Furthermore, 1,3,7-TriBDD-induced the mRNA and protein expression of *ck*Pcna, which is an indicator of excessive cell proliferation and early cancer development, thereby supporting the possibility that 1,3,7-TriBDD exposure can induce a precancerous state. Considering that TCDD is recognized as a class 1 carcinogen and tumor promotion by dioxin exposure is related to uncontrolled cell proliferation, the transcriptome results suggest that 1,3,7-TriBDD administration might also lead to excessive cell proliferation that can induce a precancerous state.

The comparisons of pathways between the 1,3,7-TriBDD- and TCDD-treated groups showed that the two compounds had impacted four pathways in the opposite direction. These pathways, which are related to breast cancer, hepatitis C, insulin signaling, and peroxisome, were mostly activated by 1,3,7-TriBDD exposure, but were suppressed by TCDD exposure. These distinct responses may have caused different phenotypic effects between the 1,3,7-TriBDD- and TCDD-treated embryos. In this study, TCDD-treated chicken embryos had shorter body and head lengths compared with the control embryos, whereas no morphological effects were observed in the 1,3,7-TriBDD-treated embryos. The mortality of chicken embryos was also higher in those treated with TCDD than in those treated with 1,3,7-TriBDD. Thus, the suppression of insulin signaling in the TCDD-treated group is possibly responsible for the increased developmental failure and morphological effects of chicken embryos.

Publication/conference presentation

1. Kanda, K., Ito, S., Koh, D.H., Kim, E.Y., Iwata, H. (2021): Effects of tris(2-chloroethyl) phosphate exposure on chicken embryos in a shell-less incubation system, Ecotoxicology and Environmental Safety, 207, 111263, doi.org/10.1016/j.ecoenv.2020.111263
2. Hoa, T.N., Li, L., Eguchi, A., Kannan, K., Kim, E.Y., Iwata, H. (2021): Effects on the liver lipidome of rat offspring prenatally exposed to bisphenol A, Science of the Total Environment, 759, 143466, doi.org/10.1016/j.scitotenv.2020.143466
3. Cho, M.K., Park, J.G., Iwata, H., Kim, E.Y. (2021): 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin prompted differentiation to $CD4^+CD8^-CD25^+$ and $CD4^+CD8^+CD25^+$ Tregs

and altered expression of immune-related genes in the thymus of chicken embryos, Ecotoxicology and Environmental Safety, 211, 111947, doi.org/10.1016/j.ecoenv.2021.111947

4. Dau, P.T., Ishibashi, H., Tuyen, L.H., Sakai, H., Hirano, M., Kim, E.Y., Iwata, H. (2021): Assessment of binding potencies of polychlorinated biphenyls and polybrominated diphenyl ethers with Baikal seal and mouse constitutive androstane receptors: Comparisons across species and congeners, Science of the Total Environment, 150631, doi.org/10.1016/j.scitotenv.2021.150631

Perspectives in future

The exposure of avian species to 1,3,7-TriBDD, a naturally occurring dioxin, may induce changes to genes involved in metabolic alterations and the precancerous state, similar to the effects of TCDD. The common effects may be triggered by AHR activation, as suggested by the induction of *ck*Cyp1a4 and 1a5. Although recent studies have focused on the effects of PBDD congeners on various organisms, the target congeners were mostly 2,3,7,8-substitutions, whereas 1,3,7-TriBDD received much less attention. The results of this study also revealed that the transcriptomic effects of 1,3,7-TriBDD are at least partially distinct from those of TCDD. This slight difference may lead to minor effects by 1,3,7-TriBDD exposure and fatal effects by TCDD exposure. Given that the risk of 1,3,7-TriBDD may be of increasing concern, further studies are necessary to understand the comprehensive effects of 1,3,7-TriBDD on various animals that inhabit coastal ecosystems.