Abstract

[Project Information]

Project Title :	Research on the Development of Methods for Evaluating the Effects of Environmental Pharmaceuticals on Fish: Establishment of Integrated Evaluation Platform Based on Environmental Analysis, Molecular Biological Analysis, and Behavioral / Reproductive Analysis
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[Abstract]

Pharmaceuticals used by humans are discharged into aquatic environments via sewage treatment plants. These are referred to as environmental pharmaceuticals, and growing concern has been raised about their impact on aquatic ecosystems, particularly on the behavior and reproduction of aquatic organisms. To address this issue, we designed a study to establish an integrated assessment framework for environmental pharmaceuticals.

This study focuses on pharmaceuticals that act on the nervous system (G protein-coupled receptor targeting drugs and antidepressants), and sets out the following three specific research objectives: (Sub-theme 1) to assess the pharmacological activity of environmental pharmaceuticals on fish receptors and to know the occurrence of their environmental concentrations; (Sub-theme 2) to identify and evaluate fish biomolecules that serve as targets of these compounds; (Sub-theme 3) to analyze the effects of environmental pharmaceuticals on fish behavior and reproduction.

The outcomes of this study are summarized as follows:

1) Using cell culture assays, we elucidated the pharmacological activity of pharmaceuticals and their metabolites on receptors derived from fish species, including medaka (*Oryzias latipes*), ayu (*Plecoglossus altivelis*), and zebrafish (*Danio rerio*).[1),2)]
2) We developed a comprehensive analytical method for the quantification of high-risk pharmaceuticals and applied it to urban river basin. [1),2)]
3) RNA sequencing and metabolomic analyses of medaka brains exposed to pharmaceuticals revealed alterations in the expression of circadian rhythm-related genes, oxidative stress responses, and changes in monoamine-related metabolites.
4) Omics-based analyses identified molecular events and pathways in the medaka brain that are likely involved in the progression from pharmaceutical exposure to behavioral abnormalities. These findings provide key components for constructing adverse outcome pathways.
5) Long-term exposure experiments were conducted in medaka to below the lowest observed effect concentration of antidepressants and antipsychotics. Reproductive assays using these individuals revealed a significant reduction in egg production.
6) In combined exposure experiments with antidepressants and antipsychotics, a decrease in egg production was observed, indicating additive effects of pharmaceuticals.
7) We developed a pharmaceutical impact assessment method using abnormal behavior in medaka, specifically surface-swimming activity, as an evaluation endpoint.
8) Exposure experiments using ayu revealed different patterns of abnormal behavior compared to medaka, suggesting species-specific behavioral responses to the same pharmaceuticals.

This study provided foundational academic insights that enable the linkage between the environmental dynamics of pharmaceuticals in river systems, molecular responses in fish, and the resulting organism-level outcomes. Such integrated understanding is essential for evaluating the ecological impacts of environmental pharmaceuticals.

[References]

1)Zhang H, Kato D, Ihara OM, Jürgens MD, Johnson AC, Chen J, Tanaka H, Ihara M. Biological-activity-based prioritization of antidepressants in wastewater in England and Japan. Environ. Sci. Technol., 2023, Volume 57, 6444-6454 (2023)

2)Zhang H, Cao M, Ihara MO, Jürgens MD, Johnson AC, Chen J, Tanaka H, Ihara I. Using Zebrafish G Protein-Coupled Receptors to Obtain a Better Appreciation of the Impact of Pharmaceuticals in Wastewater to Fish. Environ. Sci. Technol., 59(1), 92-102 (2025)

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