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Evaluation of toxicity of neonicotinoids (acetamiprid and clothianidin) by omics analysis using *Caenorhabditis elegans*

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Yuko Sakaguchi [a)], Airi Minami [a)], Yu Ikawa [a)], Takahiro Takayama [a)], Sadahiro Kawazoe [b)], Masaya Uchida [c)], Nobuaki Tominaga [c)], Koji Arizono [d)], Nobuhiro Ichikawa [a)], Koichi Inoue [a)]

a) Ritsumeikan University
b) Kyoto Women's University
c) National Institute of Technology, Ariake College
d) Graduate School of Pharmaceutical Sciences, Kumamoto University

Abstract

Neonicotinoids (NNs) are potent agonists of nicotinic acetylcholine receptors, exerting insecticidal effects by causing abnormal excitation of the nervous system. In recent years, concerns have risen regarding the effects of NNs on mammals, including humans. *Caenorhabditis elegans* (*C. elegans*), which shares a high percentage of gene homology with humans, has been widely used as a model organism for toxicity assessment. In this study, we aimed to identify the common toxicity of NNs through omics analysis, combining RNA sequencing and non-targeted metabolomics, using *C. elegans* as a model organism. L1 larvae were exposed to 100 μM acetamiprid (ACE) and clothianidin (CTD) for 24 h, and larval RNA was analyzed using next generation sequencing. For non-targeted metabolomics, larval metabolites were analyzed using LC-Q-TOF/MS. The numbers of significantly altered genes and metabolites were higher in the ACE-exposed group compared to the CTD-exposed group. These findings are consistent with our previously reported bioassay for *C. elegans*, which demonstrated greater effects in the ACE-exposed group than in the CTD-exposed group. In addition, the metabolomic results showed significantly increased expression of glutathione-related genes and metabolites in both ACE- and CTD-exposed groups, suggesting that oxidative stress is a common toxic effect of NNs. This study demonstrates the utility of *C. elegans* as a model for comprehensive toxicity assessment.

Keywords : *Caenorhabditis elegans*, neonicotinoid, acetamiprid, clothianidin, omics

I Introduction

The discovery of imidacloprid by Shinzo Kagabu, Neonicotinoids (NNs) were subsequent market introduction in the 1990s as alternatives to organophosphorus and other pesticides[1)]. Since their introduction, they have been registered as pesticides in approximately 120 countries and are now the most used pesticides globally[2)]. NNs, a generic term for chloronicotinyl pesticides based on the nicotine structure, includes seven types currently registered in Japan[3)]. These compounds have been detected in rice and other crops in Japan[4)]. Notably, the residue levels of NNs in fruits, vegetables, and tea leaves are several to dozens of times higher than those in other countries, raising concerns about potential adverse effects on human health.

NNs are potent selective agonists of insect nicotinic acetylcholine receptors (nAChRs), exhibiting insecticidal activity by causing abnormal sympathetic nerve excitation. They display a remarkably high binding affinity for insect nAChRs, with selectivity that is tens to hundreds of times higher than for mammalian nAChRs[5)]. However, studies have reported that NNs can bind to and affect mammalian nAChRs, even with low affinity[6)]. Importantly, differences observed in binding experiments between insects and mammals are not always directly relevant to toxicological outcomes[7)]. Numerous cases of nicotine-like poisoning caused by NNs, including

Corresponding author: Yuko Sakaguchi, Ritsumeikan University,
1-1-1, Nojihigashi, Kusatsu-city, Shiga 525-0058, Japan