HOKKAIDO UNIVERSITY

Title	Toxicological studies on feline cytochrome P450 associated with environmental chemical exposures [an abstract of dissertation and a summary of dissertation review]
Author(s)	Kraisiri, KHIDKHAN
Degree Grantor	北海道大学
Degree Name	博士(獣医学)
Dissertation Number	甲第14271号
Issue Date	2020-09-25
Doc URL	https://hdl.handle.net/2115/79722
Rights(URL)	https://creativecommons.org/licenses/by/4.0/
Type	doctoral thesis
File Information	Kraisiri_KHIDKHAN_abstract.pdf, 論文内容の要旨

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

学位論文内容の要旨

Abstract of the dissertation

博士の専攻分野の名称：博士（獣医学）　　氏名：Kraisiri KHIDKHAN

Name

学位論文題名

The title of the doctoral dissertation

Toxicological studies on feline cytochrome P450 associated with environmental chemical exposures

(環境化学物質への曝露に関するネコのシトクロム P450 の毒性学的研究)

Pet cats are frequently exposed to veterinary drugs and a variety of environmental compounds. They are also known to be especially sensitive to some drugs and chemical exposures. To identify their species' sensitivity and toxicity caused by these environmental exposures, the knowledge on biotransformation ability for several xenobiotics in cats is thus required. Cytochrome P450 (CYP) is one of the most dominant metabolism enzymes in phase I and can be induced by numerous compounds. The study on feline CYP isozymes expression involved in chemical exposures is necessary for the prediction of adverse effects forward to drug development and veterinary clinic medication. In this study, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and neonicotinoids are selected as the models of environmental compounds exposed to domestic cats worldwide. This present study aimed to elucidate the mRNA expression of the CYP1–CYP3 families in the cat tissues and CYP mRNA expression related to PCB and PBDE exposures, and to investigate the species differences in CYP involved in metabolism of PCBs and neonicotinoids between cats and other species. The *in vivo* exposures and *in vitro* CYP metabolism assay were conducted. Our results found that, in cats, the greatest abundance of CYP1–CYP3 (CYP1A2, CYP2A13, CYP2C41, CYP2D6, CYP2E1, CYP2E2, CYP2F2, CYP2F5, CYP2J2, CYP2U1, and CYP3A132) was expressed in the liver, but some extrahepatic isozymes were found in the kidney (CYP1A1), heart (CYP1B1), lung (CYP2B11 and CYP2S1) and small intestine (CYP3A131). Feline CYP1A1, CYP1A2 and CYP1B1 were significantly upregulated in the liver as well as in several tissues after once exposure to PCBs. However, these CYP1–CYP3 showed no significant difference in mRNA expression between control and BDE-209 exposure cats indicate that the chronic exposure of BDE-209 could not change CYP expression in the liver of cats. The study of *in vitro* CYP-mediated PCB metabolism found that the OH-PCB profiles between cats and dogs were similar and 4′OH-CB18 was major metabolite. These findings combined with *in silico* docking simulation indicated that cat CYP3A and dog CYP3A/1A1 could mainly catalyze most PCBs, particularly PCB18, while CYP1A1 in cats and CYP1A2/2B in dogs may be less players for the metabolism of some PCBs. The levels of OH-PCB formation indicate feline

CYPs have lower affinity to PCBs than those in dogs. The kinetic parameters of CYP metabolizing neonicotinoids indicate cats have particularly low CYP activity for metabolism of neonicotinoids in comparison to rats and humans. The feline glucuronidation deficiency together with all our findings suggested that PCBs and neonicotinoids may be metabolized less in cats as compared to other species.