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Title: Gene regulation mechanism of mouse drug-metabolizing enzyme CYP1A2 by nuclear receptor CAR.

Background and Purpose: CYP1A2 is one of the major drug-metabolizing enzymes responsible for drug detoxification. Activity of CYP1A2 is increased after exposure to drugs or environmental pollutants. This phenomenon, known as "enzyme induction," is a part of the biological defense system of our body. However, the regulatory mechanism of induction is not necessarily identical between humans and experimental animals. In the processes of new drug developing, safety of candidate chemicals is confirmed through examinations using experimental animals. However, even though induction is observed in experimental animals, determining whether it is occurred in humans requires information of the similarities and differences of induction mechanisms between humans and experimental animals. The objective of this study is to analyze the regulatory mechanism of the mouse *Cyp1a2* gene and clarify similarities with the human *CYP1A2* gene.

Research Outline: Enzyme activity of CYP1A2 is increased upon exposure to phenobarbital (a hypnotic), due to gene activation. In this process, nuclear receptor CAR is activated by phenobarbital, which binds to the regulatory site of the *CYP1A2* gene, resulting in gene activation. Analysis of mouse *Cyp1a2* gene revealed similarities and differences with the human *CYP1A2* gene. Human and mouse *CYP1A2* genes share very similar structures (nucleotide sequences). Previously, a single ER8-type binding site was identified in the human *CYP1A2* gene, in which CAR binds and activates. In this study, it is revealed that CAR binds to the different site in the mouse *Cyp1a2* gene, and activates it. However, the newly identified CAR binding site in mouse *Cyp1a2* gene is also ER8-type, suggesting that, despite the different location, the induction is under the control of similar mechanism to that in humans. These results suggest that mice may be a suitable animal model for predicting human CYP1A2 induction.

Future Prospects: This study focused on the binding of CAR to *CYP1A2* gene. However, it is also known the species difference of chemicals that activate human CAR and mouse CAR. It will be able to extraporate more accurately from mice to humans, if we have developed a system to analyze and evaluate species differences in CAR activation.

Reference:

Constitutive androstane receptor-responsive elements for mouse *Cyp1a2* transcriptional activation induced by constitutive androstane receptor ligands.
Drug Metabolism and Pharmacokinetics doi;10.1016/j.dmpk.2022.100485 2023