Caffeine metabolism and Cytochrome P450 enzyme mRNA expression levels of genetically diverse inbred mouse strains

Neal Addcott - CSU East Bay, Michael Malfatti - Lawrence Livermore National Laboratory, Gabriela G. Loots - Lawrence Livermore National Laboratory

1. Introduction

Caffeine is broken down in humans by several enzymes from the Cytochrome P450 (CYP) superclass of enzymes. These CYP enzymes are important in activating or eliminating many medications. The evaluation of caffeine metabolites in a patient has been proposed as a means of estimating the activity of some CYP enzymes, contributing to genetics-based personalized medicine. The frequency and distribution of polymorphisms in inbred strains of mice often mirrors the variety in genotypes found in human populations. This project hopes to determine whether four inbred strains have enough inter-strain differences in both their metabolite profiles and expression of mouse CYP enzymes to support additional investigations.

2. Background

Several polymorphic CYP proteins outside of this study’s scope have already been characterized in Caucasian populations with enough detail to warrant clinical dosing decisions based on CYP genotypes. The current understanding of CYP2A and CYP4A/3 genetics still needs more development before being applied to personalized medicine. Caffeine metabolism (specifically Paraxanthine/Caffeine ratios) serves as a clinically recognized indicator of CYP2A5 activity.

3. Methods

The following methods are described:

- **Eliminations Routes for Top 200 Prescribed Drugs**
- **Relative CYP strengths metabolizing caffeine in human liver microsomes**
- **CYP450 Enzymes**
- **Pathway Preference of Human CYP Enzymes for caffeine catalysis**
- **Overall process of project**
- **Sample gel electrophoresis of rIP/C products**

4. Results

This work represents the first steps of a larger investigation, and the BALB/cJ and DBA/2J strains have emerged as candidate model organisms for human CYP polymorphisms detectable by caffeine metabolite levels. In the next stage, eleven additional mouse strains will be examined for mRNA expression levels.

While paraxanthine was expected to be the primary metabolite, after thirty minutes theophylline was detected at similar levels. Data will need to be collected two hours after injection for a closer comparison to published paraxanthine/caffeine ratios. A 1,3,7-Trimethyluric acid standard will be prepared and checked against existing chromatogram data. A small peak near theophylline is a likely possibility.

Identified candidate mouse strains will have their mRNA sequences determined to more carefully characterize polymorphisms that could influence catalytic activity.

5. Discussion

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References


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