

## EFFECT OF PHENOBARBITAL AND SPIRONOLACTONE TREATMENT ON THE OXIDATIVE METABOLISM OF ANTIPYRINE BY RAT LIVER MICROSOMES

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The effects of pretreating rats with the inducers, phenobarbital or spironolactone, on the formation rate of the three major oxidative metabolites of antipyrine *in vitro* by hepatic microsomal fractions have been investigated. Both inducers reduced the rate of 3-methylhydroxylation of antipyrine by approximately 50%. In contrast, N-demethylation and 4-hydroxylation were enhanced 1.7-fold and 3.4-fold, respectively, in case of phenobarbital induction and 1.4-fold and 2.6-fold, respectively, following spironolactone treatment.

To elucidate the role of some cytochrome P450 isoenzymes in the production of the three major metabolites of antipyrine, the effects of form selective enzyme inhibitors on antipyrine oxidation were also studied. Troleanomycin did not alter 3-methylhydroxylation but reduced both N-demethylation and 4-hydroxylation of antipyrine in microsomes from induced rat liver. Cimetidine and chloramphenicol decreased the rate of formation of all three metabolites in microsomes from induced and uninduced animal livers as well. Chloramphenicol seemed to be the most potent inhibitor of *in vitro* antipyrine oxidation. -Methyldopa significantly enhanced the rate of formation of 4-hydroxyantipyrine and slightly reduced the rate of N-demethylation and 3-methylhydroxylation.

According to the data obtained with microsomes from uninduced rat livers, the formation of the three major metabolites of antipyrine is extensively mediated by CYP2C11/C6. In microsomes from induced animal liver, CYP2B and CYP3A may contribute to both N-demethylation and 4-hydroxylation of antipyrine.

**Key words:** antipyrine, phenobarbital, spironolactone,  $\alpha$ -methyldopa, cytochrome P-450, liver microsomes, rat

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