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STUDIES ON DRUG METABOLISM BY USE OF  
ISOLATED RAT LIVER CELLS

by

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## ABSTRACT

The metabolism of drugs in freshly-prepared isolated rat liver cells has been studied. These cells efficiently metabolize drugs and do not require added co-factors such as NADPH or UDP-glucuronic acid. Some substrates of the liver microsomal monooxygenase system, such as  $\alpha$ -*l*-acetylmethadol and *d*-propoxyphene, are oxidized at the same rate in cells as in liver homogenate fractions fortified with NADPH. Other substrates, such as butamoxane and ethinimate are oxidized at a slower rate with cells than with homogenate fractions. In contrast, intact cells hydroxylate amphetamine faster than do homogenized liver preparations. The rate of both amphetamine and butamoxane hydroxylation is the same in isolated cells as in the perfused liver. Typical monooxygenase inhibitors, such as DPEA (2,4-dichloro-6-phenylphenoxyethylamine) and SKF 525A (diethylaminoethyl-diphenylpropylacetate) are effective inhibitors of oxidative drug metabolism in the isolated cells. The cellular concentration of cytochrome P450 and the rate of oxidative drug metabolism are increased in cells isolated from phenobarbital (PB)- and  $\beta$ -naphthoflavone-treated rats.

In addition to characterizing the ability of isolated hepatocytes to metabolize drugs, the metabolism of some drugs has been more thoroughly studied with the cells. These results have been compared with drug metabolism in the intact rat and with metabolism in liver

homogenate fractions. The results of these comparative studies indicate that the isolated hepatocytes are a more reliable predictor of drug metabolism in the intact rat than are subcellular liver fractions. For example, the metabolism of ethinimate in intact cells and the effects of other drugs on its metabolism correlates very well with metabolism in vivo. In addition, the effect of PB on the N-demethylation of propoxyphene in the intact cells correlates with its effect in the intact rat, but does not correspond with what is observed with liver homogenate preparations. Another example is the stereospecificity of the enzymatic reduction of nabilone, a synthetic keto-cannabinoid. With both isolated cells and the intact rat, only the S-alcohol isomer is formed. However, with 9000 x g liver supernate, the R-isomer is also found. In addition, some of the unusual properties of amphetamine aromatic hydroxylation which are seen in vivo have now been observed in the isolated liver cells.