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INHIBITION OF SOME MICROSOMAL DRUG-METABOLIZING ENZYMES BY INHIBITORS OF CHOLESTEROL BIOSYNTHESIS

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Abstract—Microsomal enzymes are observed to help some stages of cholesterol biosynthesis: these enzymes act similarly to those responsible for the metabolism and for the consequent inactivation of several drugs e.g. pentobarbital and carisoprodol. Some well-known inhibitors of the cholesterol synthesis like triparanol and carisoprodol are proved to have an inhibitory action also on the *in vitro* and *in vivo* metabolism of both pentobarbital and carisoprodol.

A VARIETY of liposoluble drugs are metabolized by enzymes localized in the liver microsomes. These enzymes have a common requirement of TPNH (reduced triphosphopyridinnucleotide) and oxygen and their activity is inhibited by SKF 525 A (β-diethylaminoethyldiphenylpropylacetate HCl). On the other hand the biosynthesis of cholesterol occurs in the liver and some steps take place in the liver microsomes requiring TPNH and oxygen.

Dick *et al.* recently reported that a chronic administration of SKF 525 A lowered plasma cholesterol levels in dogs.[1]

The purpose of the present study is to investigate a possible inhibitory action of the two most representative inhibitors of cholesterol biosynthesis (triparanol and benzmalacene) on drug metabolism in liver microsomes.

EXPERIMENTAL

Male rats of the Sprague–Dawley strain, weighing about 70 g were used. The determination of the metabolism of the drugs in the microsomal preparation was carried out as previously reported.[2–4] Triparanol was dissolved in propylenglycol and diluted with water before being added to the incubation mixture. The final concentration of propyleneglycol was 0·5%, and no inhibition of the enzyme activity was observed with this concentration. Sodium benzmalacene was dissolved in distilled water.

The final concentrations of pentobarbital, hexobarbital, strychnine, meprobamate and carisoprodol in the incubation mixtures were 2×10^{-4} M, 4×10^{-4} M, 2×10^{-4} M, 3×10^{-4} M and 3×10^{-4} M, respectively.

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RESULTS

The concentrations of triparanol and benzmalacene causing a 50 per cent inhibition of the drug metabolism are given in Table 1. Triparanol strongly inhibits the metabolism of pentobarbital, carisoprodol and meprobamate, while it has only a weak effect on the hexobarbital metabolism. Benzmalacene generally has a somewhat more potent inhibitory action than triparanol. It inhibits also the metabolism of strychnine.

TABLE 1. INHIBITION OF *in vitro* METABOLISM OF PENTOBARBITAL, HEXOBARBITAL, STRYCHNINE, CARISOPRODOL AND MEPROBAMATE BY TRIPARANOL AND BENZMALACENE

Substrate	Inhibitor (concentration causing 50% inhibition) Triparanol	Benzmalacene
(1) Pentobarbital	$1{\cdot}9 \times 10^{-4}$	—
(2) Hexobarbital	$8{\cdot}1 \times 10^{-4}$	—
(3) Strychnine	—	$6{\cdot}8 \times 10^{-4}$
(4) Carisoprodol	$1{\cdot}8 \times 10^{-4}$	$8{\cdot}0 \times 10^{-5}$
(5) Meprobamate	$1{\cdot}6 \times 10^{-4}$	$6{\cdot}1 \times 10^{-5}$

TABLE 2. POTENTIATION OF PENTOBARBITAL HYPNOSIS AND CARISOPRODOL PARALYSIS BY TRIPARANOL AND BENZMALACENE

(Female rats, weighing about 200 g were used; 25 mg/kg of pentobarbital or 180 mg/kg of carisoprodol were injected intraperitoneally 20 min after administration of triparanol or benzmalacene. The numerals in the brackets indicate the numbers of animal used.)

	Dose (mg/Kg)	Pentobarbital hypnosis (min)	Carisoprodol paralysis (min)
(1) Control		83 ± 5·6 (10)	67 ± 6·8 (10)
(2) Triparanol	75	149 ± 7·5 (10)	163 ± 10·4 (10)
(3) Benzmalacene	75	230 ± 10·7 (10)	278 ± 13·5 (10)

Inhibitions of *in vivo* metabolism of pentobarbital and carisoprodol were studied by the potentiation of pentobarbital hypnosis and carisoprodol paralysis. Benzmalacene increased markedly the pentobarbital hypnosis and carisoprodol paralysis; triparanol is also efficient though more weakly ($p < 0{\cdot}001$)

DISCUSSION AND CONCLUSION

A variety of drugs are known to be inhibitors of drug metabolism, among the most potent and well-known being SKF 525. On the other hand, SKF 525 is also an inhibitor of the biosynthesis of cholesterol. The exact mechanism which produces the

inhibition of the cholesterol biosynthesis by triparanol and benzmalacene is not yet completely clear. Triparanol and benzmalacene cause 50 per cent inhibition of the activity of the microsomal drug metabolizing enzymes at a range of 1×10^{-4}–5×10^{-4}. On the other hand, triparanol and benzmalacene stimulate, like SKF 525 A, the metabolism of hexobarbital, pentobarbital, meprobamate, carisoprodol and strychnine 48 hr after their administration.[5-6]

These results strongly suggest the presence of some similar process between drug metabolism and cholesterol biosynthesis in liver microsomes.

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