Implications of SAM in estrogen metabolism

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Both natural and synthetic estrogens can interfere with bile formation mechanisms by inducing intrahepatic cholestasis or cholesterol supersaturation of bile (Kern et al., 1978).

Two main mechanisms seem to be responsible for the toxic effects of estrogens: first, the capability to form some "reactive" metabolites with a property of irreversible binding to microsomal proteins (Nelson et al., 1976); second, their capability to reduce the fluidity of canalicular membranes by modification of the cholesterol/phospholipid ratio. As a consequence, the activity of Na^+-K^+-ATPase, the enzyme responsible for the active canalicular secretion of sodium, is reduced (Simon et al., 1980).

The estrogen irreversible binding to liver microsomes seems to be subordinate to the hydroxylation at position C_2 (Kappus et al., 1973); the catecholestrogens thus formed would be then transformed, in the presence of oxygen and NADPH, into reactive metabolites by a cytochrome P-450 mediated reaction (Nelson et al., 1976). According to *in vitro* observations by Kappus and Bolt (1974), methylation of catecholestrogens by SAM prevents the irreversible binding of 17α-ethinylestradiol (EE) reactive metabolites to liver microsomal proteins. This observation has been confirmed *in vivo* by Stramentinoli et al. (1979; 1981), who demonstrated that a simultaneous administration of EE and SAM significantly reduces the binding to liver microsomal proteins (Fig. 1), increasing the methylation of EE catechol derivatives. Evidence was also given (Stramentinoli et al., 1979; 1981) that SAM treatment was able not only to prevent EE-induced cholestasis, but also to antagonize the EE-induced cholesterol supersaturation of bile.

E. Usdin et al., *Biochemistry of S-Adenosylmethionine and Related Compounds*

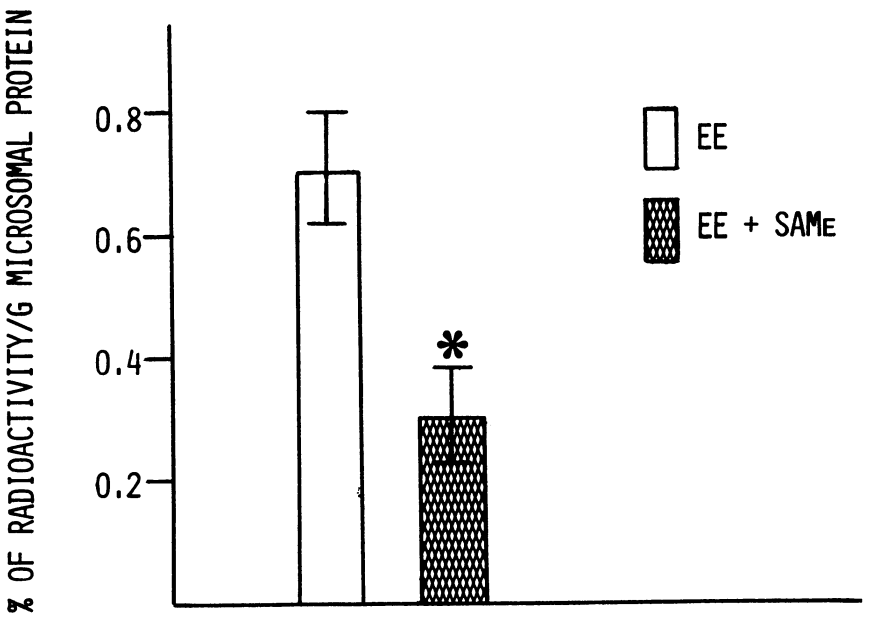

Fig. 1. Radioactivity firmly bound to rat liver microsomes 48 h after administration of 6,7-^{3}H-EE (5 µCi). Values are expressed as mean ± S.E. for 5 animals. *P<0.05

Aim of the present study was to evaluate whether also in man SAM can antagonize EE-induced impairment of bile secretion. For this purpose, two different experimental models have been selected, designed to determine SAM anti-lithogenic property and to study its anti-cholestatic effect, respectively. In the first case, 5 non-obese subjects with indwelling T-tubes volunteered for the study. The T-tube had been inserted in the common duct during cholecystectomy, performed more than two weeks before the experiment, and its external arm had been closed for at least 10 days in order to restore enterohepatic bile circulation (Nakayama and Van der Linden, 1974). At the time of this study, liver function tests gave normal results and bile culture was negative for aerobic and anaerobic bacteria. All patients then received a standard diet and no other drugs over the treatment period. On different days and after an overnight fast, subjects were given either 200 µg of EE or same dose of EE plus SAM. The latter was injected i.m. in two doses of 100 mg each one h before and 4 h after EE administration.