PROSTAGLANDIN SYNTHETASE-DEPENDENT METABOLISM OF N-ALKYL COMPOUNDS

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We have recently shown that benzo (a) pyrene, + trans-7, 8-dihydroxy-7, 8-dihydrobenzo (a) pyrene and 7, 12-dimethyl benzanthracene are metabolized during prostaglandin biosynthesis. We have now investigated the metabolism of several N-alkyl compounds during prostaglandin biosynthesis by ram seminal vesicle (RSV) microsomal fraction. With most of the substrates, rates of RSV microsomal N-dealkylation were either comparable to or significantly greater than N-dealkylation rates obtained using rat liver microsomes fortified with NADPH. In addition, RSV microsomal N-delakylation occured at much lower protein concentrations and was temperature-independent (20-37°C) when compared to the reaction catalyzed by rat liver microsomes. N-dealkylation by RSV microsomes was completely dependent on enzyme and fatty acid and could be inhibted by indomethacin or phenylbutazone, inhibitors of prostaglandin synthetase. In addition to arachidonic acid, dealkylation was elicited by 15-hydroperoxy arachidonic acid, cumene hydroperoxide and tert-butyl hydroperoxide; these latter reactions were not inhibited by prostaglandin synthetase inhibitors but did require the presence of microsomal fraction. The metabolism of N-alkyl compounds during the biosynthesis of prostaglandins may provide an alternate oxidative pathway to the cytochrome P_{450} mono-oxygenases. Thus, it appears that prostaglandin synthetase system may play a significant role in the disposition of these xenobiotics.