DOES ACETYLSALYCILIC ACID INTERFERE WITH LIVER DIMETHYLBENZANTHRACENE(DMBA)- METABOLISM? STUDY IN A RAT MODEL OF DMBA-INDUCED MAMMARY CARCINOGENESIS

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Growing evidences support the regular use of aspirin and other nonsteroidal anti-inflammatory drugs as effective chemopreventive agents for breast cancer. A recent study showed that acetylsalicylic (ASA) and salicylic acid (SA) both inhibit the formation of dimethylbenzanthracene (DMBA)-induced rat mammary tumours, suggesting as a possible mechanism of salicylate chemopreventive action the inhibition of tumour angiogenesis. To exert its carcinogenic effect, DMBA undergoes bioactivation, which involves oxidation by hepatic and extrahepatic phase I enzymes, especially cytochrome P450 (CYP)1A.. Cancer chemopreventive agents can modulate both phase I and phase II enzymes involved in the bioactivation or detoxification of carcinogens, respectively, and antioxidant enzymes as well. The aim of this work was to investigate the effect of a pre-treatment with ASA on: CYP1A activity and expression; CYP-mediated oxidative metabolism of DMBA; selected conjugative and antioxidant enzyme activity. **Methods** Seventy-two 45 day-old female Sprague-Dawley rats were randomly divided into 4 groups and treated *per os* as follows: control (olive oil); ASA (50 mg/ml saline/rat for 21 days); DMBA (10 mg/ml olive oil/rat at days 7, 14, and 21); DMBA+ASA (treated according to DMBA and ASA treatment schedule). Six animals from each group were sacrificed 24 hr after each DMBA administration and the hepatic subfractions were isolated. CYP1A1-related O-dealkylation of either ethoxy- or methoxyresorufin, CYP1A1/2 apoprotein levels, and the extent of the *in vitro* metabolism of [^{3}H]DMBA were measured. The assayed phase II and antioxidant enzyme activities included 1-naphthol-uridindiphosphoglucuronyl-transferase (UGT), glutathione S-transferase (GST) and DT-diaphorase; reduced glutathione content (GSH) was also determined. **Results** At the different time points, DMBA significantly increased the level and activity of CYP1A as well as the extent of its own metabolism. However, these changes were not affected by ASA administration. Conversely, ASA was associated with considerable enhancement of the DMBA-mediated time-dependent increase in GSH levels and DT-diaphorase activity, reaching statistical significance 24 h after the second and third administration of the carcinogen, respectively. **Conclusion**. The present data suggest that ASA could exert its beneficial effect on DMBA-induced mammary carcinogenesis by modulation of liver antioxidant defence systems. The increased GSH content and DT-diaphorase activity may lower the amount of the ultimate carcinogen that can react with target sites of the mammary gland.