

STUDIES ON NAD(P)H DEHYDROGENASE AND ITS ROLE IN VITAMIN K DEPENDENT CARBOXYLATION. R. Wallin. Inst. Medical Biology, University of Tromsø, Tromsø, Norway.

A simple two-step method has been established for the purification of NAD(P)H dehydrogenase (DT diaphorase) from rat liver by affinity chromatography. The same method has been used to remove selectively the enzyme from the detergent-solubilized, microsomal vitamin K-dependent carboxylating system. The removal of NAD(P)H dehydrogenase inactivated the system, but the activity is restored if purified enzyme is added back to the system.

EFFECT OF WARFARIN, WARFARIN ENANTIOMERS AND DEFIBRASE ON LEWIS LUNG CARCINOMA METASTASIS GROWTH IN MICE. M. B. Donati, A. Poggi, L. Mussoni, L. Kornblihtt, G. de Gaetano and S. Garattini. Istituto di Ricerche Farmacologiche 'Mario Negri', Milano, Italy.

The Lewis Lung Carcinoma (3LL) is a spontaneously metastasizing tumor, the development of which is accompanied by marked hemostatic changes. Acceleration of labelled fibrinogen turnover and fibrin accumulation at the tumor and metastasis sites have been observed in 3LL bearing mice. Both the number and the weight of lung metastases were significantly lower in mice anticoagulated with racemic sodium warfarin during the whole tumor development period (prothrombin complex activity around 20%). This treatment had less effect on the primary tumor. The anti-metastatic effect was slightly greater with larger doses of warfarin, which lowered the prothrombin complex activity to less than 5%. Continuous anticoagulation also protected the animals from pulmonary growth of blood-borne tumor emboli following intravenous injection of 3LL cells. This effect appeared to be closely associated with the anticoagulant activity of warfarin; indeed experiments performed with the resolved warfarin enantiomers showed that R-warfarin had virtually no anticlotting activity in mice and did not modify the metastatic growth of 3LL cells; the opposite was true for S-warfarin.

Lung metastasis growth was increased in mice kept defibrinogenated during the whole period of tumor development by treatment with batroxobin; in contrast, in mice kept defibrinated only during the period of metastasis growth, with or without surgical removal of the primary tumor, metastasis formation was slightly decreased. This suggests that fibrin may play different roles in various phases of metastatic spreading of the same tumor.

EFFECT OF BEZAFIBRATE ON BLOOD COAGULATION AND DRUG INTERACTION WITH PHENPROCOUMON. R. Zimmermann, A. Hoffrichter, E. Walter, P. D. Lang, W. Ehlers, K. Andrassy, G. Schlierf and E. Weber. Medizinische Universitätsklinik, Heidelberg, G.F.R.

In addition to their effect on lipids clofibrate and related drugs can influence platelet function and fibrinolytic activity. Interaction of these drugs with coumarin anticoagulants may induce hemorrhagic complications. Therefore the effect of a new hypolipemic agent (bezafibrate) on blood coagulation and components of the fibrinolytic enzyme system was investigated. 15 patients on long term treatment with phenprocoumon received bezafibrate (450 or 600 mg daily) for 4 weeks. Evaluation of platelet function demonstrated a reduced platelet aggregation induced by collagen ($p < 0.05$) and prolongation of bleeding time ($p < 0.05$), dependent on the given dose. Plasma fibrinogen was reduced moderately. Examination of the fibrinolytic activity yielded a shortened euglobulin clot lysis time ($p < 0.05$) but no changing of inhibitors. Serum level of phenprocoumon and bezafibrate were determined to obtain data about the mechanism of drug interaction. After reduction of the phenprocoumon dose by 20.6 or 28.7% the serum phenprocoumon levels decreased by 9.3 and 30.6%, respectively. Hypoprothrombinemia was maintained ($p < 0.05$). The results support the hypothesis, that hypolipemic drugs such as bezafibrate augment the anticoagulant response to phenprocoumon by increasing the affinity of the receptor site for coumarin and not by effecting the rate of metabolism.