PREVENTION BY SULOCTIDIL OF SPONTANEOUS PLATELET AGGREGATES IN RATS. R.N. Saunders, T.S. Burns and M.R. Stelzer. Searle Laboratories, Skokie, Illinois, U.S.A.

Atherosclerosis and cerebrovascular disease have been reported by Wexler and True (Circ. Res. 12: 659, 1963) to occur in retired breeder rats but not in virgin rats of the same age. We have discovered that retired breeder (RB) male rats have spontaneous circulating platelet aggregates (CPA) as determined by the method of Wu and Hoak (Lancet 2: 924, 1974). These CPA respond to therapy with clinically proven antiplatelet drugs. Suloctidil (S) [1-(4-isopropylthiophenyl)-2-n-octylamino propanol, Continental Pharma, Brussels] administered for 8 days at 100 mg/kg i.g. showed a significant reduction in CPA from 0.76 ± 0.05 (S.E.M.) to 0.92 ± 0.03 (where 1.0 indicates no CPA). In these same rats, the endogenous platelet 5-HT level was significantly ($P < 0.01$) lowered to 0.88 ± 0.04 (S.E.M.) $\mu\text{g}/10^9$ platelets compared to control values of 1.66 ± 0.08 $\mu\text{g}/10^9$ platelets. Plasma 5-HT levels were not altered. In vitro rat platelet 5-HT uptake is inhibited 50% by S at $6.4 \times 10^{-6}\text{M}$ in platelet-rich plasma. In rat platelets with labeled 5-HT pools, 5 min incubation with S at 10^{-5}M resulted in significantly ($P < 0.01$) greater release at 10, 20 and 30 sec after the addition of 2U/ml of thrombin. This suggests that S may decrease uptake as well as increase release of platelet 5-HT. The reduction of endogenous platelet 5-HT levels by S may be related to its observed platelet aggregate prevention activity.

PLASMA ADPase ACTIVITY IN MYOCARDIAL ISCHEMIA. A. du P. Heyns, C.J. Badenhorst, F.P. Retief, P.H.T. Kleynhans and G.M. Potgieter. University of the Orange Free State, Bloemfontein, South Africa.

Adenine nucleotides play a key role in platelet aggregation and in the autoregulation of myocardial perfusion. Low Km ADPase activity in plasma and accumulation of ADP catabolic products were investigated in patients with myocardial ischaemia and necrosis.

ADPase activity was assayed by incubation of $2\mu\text{M}$ ^{14}C -ADP in plasma at 37°C . Enzymatic reactions were terminated by heat, radio-active nucleotides separated by high voltage electrophoresis and quantitated. ADPase activity was expressed as pmol ^{14}C -ADP catabolized per minute as assayed by two point substrate concentration analysis.

^{14}C -ADP was catabolized in a single exponential manner. The breakdown products AMP, adenosine, inosine and hypoxanthine were detected. Mean ADPase activity of 25 normal males was $102 \pm \text{SD } 15$ and 15 normal females $85 \pm \text{SD } 13$. In the immediate postinfarction period 25 patients had a significantly ($P < 0.01$) increased plasma ADPase: 127 ± 40 . ADPase was also significantly increased in the patients with crescendo angina (mean $131 \pm \text{SD } 42$) ($P < 0.01$). ADPase levels were higher in the coronary sinus than in peripheral blood of the same subject. In the rat heart $>80\%$ of total ADPase activity was located in the cytosol fraction after differential centrifugation of whole heart homogenate.

Low Km ADPase activity is increased in myocardial ischaemia. The enzyme is released in anoxia. It thus may be a measurement of the well known metabolic pathway leading to adenosine accumulation in ischaemic heart muscle.

SELECTIVE INHIBITION OF PLATELET AGGLUTINATION AND AGGREGATION BY AROMATIC AMIDINO COMPOUNDS. J.D. Geratz, R.R. Tidwell, K.M. Brinkhous and S.F. Mohammad. University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina, U.S.A.

A series of aromatic amidino compounds were investigated for their inhibitory effect on platelet agglutination and platelet aggregation. Agglutination of fresh or fixed human platelets was produced by bovine plasma or by human plasma in combination with ristocetin, while aggregation of fresh platelets was induced by ADP, thrombin or collagen. Highly effective inhibitors were found for both types of platelet clumping, but there was no parallelism between the inhibitory activities in the two test systems. 5-(5-Amidino-2-benzimidazolyl)-2-(4-hydroxybenzene)benzimidazole suppressed agglutination exclusively. Pentamidine, on the other hand, strongly blocked the aggregation reactions, but did not interfere with agglutination, even at high concentrations. Compounds which inhibited aggregation also prevented the liberation of serotonin from the platelets.

This investigation has led to the identification of new specific inhibitors of platelet agglutination and aggregation which can serve an important role in future studies of the two processes. The exact mode of interaction between amidines and platelets is still being explored. In the case of agglutination, inhibition most likely occurred at the level of binding of ristocetin cofactor to the platelet membrane. In the case of aggregation, however, interference could have taken place at the membranes or in the cytoplasm and could have been enzymatic or non-enzymatic in nature.