## 1799

**VASOCONSTRICTION IN RESPONSE TO HUMAN PLATELET-VESSEL WALL INTERACTIONS.** J.M. Van Nueten (1), W.J. Janssens (1) and F. De Clerck (2). Department of Pharmacodynamics (1) and Laboratory of Haematology, Department of Life Sciences (2), Janssen Pharmaceutica Research Laboratories, B-2340 Beerse, Belgium.

Human blood platelets, stimulated with thrombin, induced contractions of isolated basilar artery segments of the dog. These platelet-mediated vascular contractions were inhibited in a concentration-dependent way by flunarizine, a $Ca^{2+}$-entry blocker, selective for vascular tissues. This inhibition increased gradually as a function of time after contact with flunarizine to reach its maximum after 60-90 min. Biochemical and pharmacological analyses, using the 5-$HT_2$-serotonergic antagonist ritanserin, the thromboxane $A_2$/prostaglandin endoperoxide antagonist BM 13.177 and the fatty acid cyclo-oxygenase inhibitor suprofen, showed that 5-hydroxytryptamine and prostanoids (thromboxane $A_2$, prostaglandine endoperoxides) were the main mediators involved. They further suggested amplification between 5-hydroxytryptamine and prostanoids at the vascular level.

| | Min(1) | $IC_{50}$ M(2) |
|---|---|---|
| Flunarizine | 90 | $5.5 \times 10^{-7}$ |
| Ritanserin | 30 | $2.2 \times 10^{-7}$ |
| BM 13.177 | 30 | $2.5 \times 10^{-7}$ |
| Suprofen | 30 | $\leq 10^{-5}$ |

(1) Incubation period; (2) Inhibition of platelet-mediated vascular contractions.

This study demonstrates that 5-hydroxytryptamine, acting in concert with thromboxane $A_2$ and/or prostaglandine-endoperoxides, is responsible for the vasoconstrictor effects of aggregating platelets. It further indicates that influx of calcium ions is involved in these vasoconstrictor responses.

## 1800

**PLATELET-MEDIATED REDUCTION OF PERIPHERAL TISSUE PERFUSION IN THE CAT : SEROTONIN AND PROSTANOIDS ARE CAUSAL VASOACTIVE MODULATORS.** A. Jageneau (1), W. Loots (1), A. Nevelsteen (2) and F. De Clerck (1). Laboratory of Haematology, Janssen Pharmaceutica Research Laboratories, Beerse, Belgium (1) and Department of Cardiovascular Surgery, University Clinic Gasthuisberg-St. Raphael, Leuven, Belgium (2).

In cats, a femoral artery was ligated in order to mobilize a collateral circulation in the hind leg, leaving the contralateral artery intact. Graded infusions of collagen (50 to 400 µg/kg) in the aorta above the bifurcation reduced the blood flow, mainly in the collateral circulation (> 80 %). Plasma 5-HI and $TXB_2$ increased in local arterial blood. Ketanserin or ritanserin ($S_2$-receptor blockade, 0.63 mg/kg I.V.) and dazoxiben or R 68070 ($TXA_2$ synthetase inhibition, 5 and 1.25 mg/kg I.V.) reduced (> 50 %, $p < 0.05$) the collagen-induced loss of tissue perfusion. Indomethacin (10 mg/kg I.V.) and prazosin (0.1 mg/kg I.V.) were ineffective. The effect of $TXA_2$ synthetase inhibitors was annihilated by indomethacin, suggesting that their activity is linked to a reorientation of arachidonic acid metabolism to vasodilating prostanoids rather than to an inhibition of the production of vasoconstrictive cyclo-oxygenase products. By contrast, combined treatments with ketanserin/indomethacin or ketanserin/R 68070 remained effective. Reserpine/PCPA treatment also prevented the collagen-induced changes in perfusion. This study demonstrates 1) oversensitivity of collaterals to platelet products; 2) serotonin to be the causal vasoconstrictive mediator; 3) effective modulation by $S_2$-receptor blockade and by vasodilating prostanoids produced after inhibition of $TXA_2$ synthetase.

## 1801

ENDOTHELIUM-INDEPENDENT PARTIAL AGONISTIC ACTIVITY OF VASOPRESSIN IN THE RAT COMMON CAROTID ARTERY. Z.S. Katušić and M.K. Krstić. Department of Pharmacology, Medical faculty, Belgrade, Yugoslavia.

It has been shown that vasopressin causes endothelium-dependent relaxations of the canine basilar artery, suggesting that increased circulating concentrations of vasopressin can produce redistribution of the blood from the peripheral to the cerebral circulation (Katušić et al., 1984). The present experiments were done to examine effect of vasopressin on the rat peripheral arteries. The experiments were performed on rings (4 mm long) of aorta, common carotid and renal arteries. The arteries were placed in Krebs-Ringer-bicarbonate solution gassed with 95%$O_2$-5%$CO_2$ gas mixture and kept at 37°C. In certain rings the endothelium was removed mechanically by gentle rubbing of the intimal surface. Isometric tension was continously recorded (IPM electronic). Vasopressin (10-11 to 3x10-8 M) caused concentration-dependent contraction being full agonist in aorta and renal artery, but partial agonist in common carotid artery. After removal of endothelium vasopressin-induced contractions were not significantlly afected in any of the tested arteries. Cyclooxygenase inhibitor indomethacin (10-5 M; contact time = 40 min) did not affect partial agonistic activity of vasopressin in common carotid artery. This results indicate that partial agonistic activity of vasopressin in common carotid artery is not related to increased production of "EDRF" or prostacyclin from endothelium. In addition, our findings are consistent with the hypothesis that vasopressin may contribute to redistribution of the blood flow from the peripheral to the cerbral circulation.

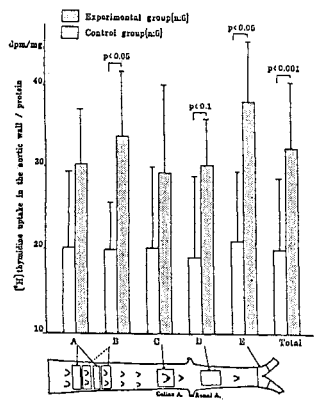
Z.S. Katušić, J.T. Shepherd and P.M. Vanhoutte. Circ. Res., 55: 575-579, 1984.

## 1802

ENDOTHELIAL CELL INJURIES AND SMOOTH MUSCLE CELL PROLIFERATION INDUCED BY MATERIALS RELEASED FROM PLATELET-RICH THROMBUS IN VIVO. Y.Asada, T. Hayashi, A. Sumiyoshi. Department of Pathology, Miyazaki Medical Collage, Miyazaki, Japan

It is widely held that the disturbance in the integrity of the arterial endothelium may lead to the development of arteriosclerosis and many factors have been postulated to cause the endothelial injury, such as hemodynamic stress, anoxia, platelet-releasing materials, and so on. However, whether any of these is important for endothelial injury is unclear. We studied whether the released products from activated platelets and/or thrombi could cause endothelial damage and proliferation of smooth muscle cells in large vessels in vivo.

Polyethylene tubing was inserted into the ascending aorta of rabbits via the common carotid artery and placed for one, 4, and 24 weeks continuously to induce vessel wall injury and thrombotic events. Then the direct non-injured segments from the descending thoracic and abdominal aorta was morphologically examined, and $^3$H-thymidine incorporation into the arterial wall was also examined. The descending aortas of experimental rabbits showed endothelial damage and increased mitoses of endothelial cells. Modified smooth muscle cells were noted in the subendothelial layer, and $^3$H-thymidine incorporation into the intima and media significantly increased in the experimental group at one week(Fig.). At 24 weeks, the intimal thickening with smooth muscle cell proliferation was also found.




This experiment indicates that materials released from the activated platelets and/or thrombi into the circulation can cause endothelial damage and smooth muscle cell proliferation and intimal thickening at downstream and remote aortic segments.