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ORAL ADMINISTRATION OF EICOSAPENTANOIC ACID (EPA) STIMULATES PRODUCTION OF PROSTACYCLIN BY RAT AORTA.
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Prostacyclin (PGI_2) which is mainly produced in blood vessels has the most potent platelet antiaggregatory activity of any substance yet found. It is therefore thought that PGI_2 is a preventive agent for cardiovascular diseases (CVD). We found that EPA orally administered to rats stimulated rat thoracic aorta to produce a PGI_2-like substance at 3 times normal levels. While there are several reports suggesting that EPA may contribute to the prevention of CVD by inhibiting platelet functions and improving plasma lipid concentrations, this is the first report that shows the relationships between orally administered EPA and PGI_2-like substance production from aorta. METHODS: Two groups of Wistar rats were fed either a normal diet (group A) or a normal diet plus 74% pure EPA, 60 mg/kg/day (group B), for 8 weeks. Thoracic aortas were excised, cut into rings, and incubated in 50 mM Tris-HCl buffer, pH 7.5, for 10 min. The activity of the PGI_2-like substance was measured by inhibition of human platelet aggregation. Platelet aggregability of rats in both groups was also checked with ADP as an aggregant. RESULTS: The rate of production of the PGI_2-like substance by the aortas of group B was 4.0±1.4 ng/mg wet aorta/10 min (calibrated with authentic Na-PGI_2), while that of group A was 1.4±0.5 ($P<0.001$). Platelet aggregability was depressed in group B rats. There was no significant difference in concentrations of plasma lipids such as total and HDL-cholesterol, triglycerides, and phospholipid. DISCUSSION: It has been suggested that EPA could prevent CVD through its anti-aggregatory property. Now we suggest a new possibility that EPA could prevent CVD by stimulating blood vessels to produce more PGI_2-like substance as well as by inhibiting platelet aggregation directly.

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ANTITHROMBOTIC AND OPPOSITE EFFECTS OF DRUGS INFLUENCING THE PROSTAGLANDIN SYSTEM.
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The prostaglandin metabolites prostacyclin (PGI_2) and thromboxane affect the aggregation of platelets and their interaction with the vessel wall.An increase of the PGI_2 availability or inhibition of the thromboxane synthesis may induce antithrombotic activity.

The antithrombotic effects of some drugs influencing the prostaglandin metabolism were investigated therefore in 220 rabbits.Arterial and venous thrombus formation was produced in a standardized experimental model of silver nitrate induced thrombosis.The following substances were examined: 1.PGI_2 20 ng/kg/min,2.PGI_2 10 ng/kg/min,3.a substance which increases the PGI_2 availability (BAY g 6575) 10 mg/kg,4.the thromboxane synthetase inhibitor UK-37,248-01 ,5.BAY g 6575 in combination with aspirin 10 mg/kg and 6.BAY g 6575 and aspirin 50 mg/kg. A reduction of the arterial and venous thrombus growth could be observed after treatment with 1.PGI_2 20 ng/kg/min (arterial system:-74%, significant [s],venous system:-64%,s), 2.PGI_2 10ng /kg/min (-34%,s,-34%,s), 3.BAY g 6575 (-50%,s,-75 %,s), 4.UK-37,248-01 (-41%,s,-36%,s), 5.BAY g 6575 in association with aspirin 10 mg/kg (-41%,not s, -50%,ns) and 6.BAY g 6575 and aspirin 50 mg/kg (-22%,ns,-21%,ns).

Our data suggest that PGI_2 and drugs increasing the availability of PGI_2 induce a pronounced and significant antithrombotic activity.A less efficient reduction of thrombus formation can be expected after inhibition of thromboxane synthesis.The decrease of the antithrombotic property of BAY g 6575 when combinated with aspirin suggests an instability of the antithrombotic activity of substances acting by influencing the prostaglandin metabolism.

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PROSTACYCLIN PRODUCTION BY AUTOGENOUS VENOUS GRAFTS IN DOGS.
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Arteries are capable of producing significantly larger quantities of prostacyclin than veins. Experiments were designed to compare the production of prostacyclin by venous autografts to that of normal veins and arteries, and to test the hypothesis that prostacyclin production by the vessel wall is related to blood pressure and flow. In 20 dogs a segment of jugular vein was interposed into the carotid system; a sham dissection was done on the opposite side. Six weeks later specimens of venous autograft, jugular vein and carotid artery were taken for histology and radioimmune assay of prostacyclin. "Arterialized" vein grafts showed prominent intima lined by endothelium, medial smooth muscle proliferation and fibrotic proliferation in adventitia. Spontaneous and arachidonic acid stimulated prostacyclin production was not significantly different in venous autografts and jugular veins. Significantly larger amounts of prostacyclin were synthesized by the carotid artery; table shows mean ± S.E. in ng/ml.

	Venous autograft	Jugular v.	Carotid a.
Spontaneous	1.5±0.3	1.5±0.2	4.5±0.6
Stimulated	3.7±1.1	4.0±0.4	15.7±1.1

We conclude that the histological and rheological changes in vein grafts do not affect prostacyclin production. While normal veins never develop atheroma, atherosclerosis is prevalent in venous autografts. The above may be explained in part by the impairment of one of the vascular defense mechanisms, namely the decreased prostacyclin production in venous grafts.

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INCREASED VASCULAR PGI_2-FORMATION AND INCREASED PLASMA 6-OXO-$PGF_{1\alpha}$ AFTER CALCITONIN IN HUMAN AND EXPERIMENTAL ANIMALS.
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5 normolipemic minipigs treated daily for 28 days with 40µg/kg h-calcitonin synthetized in thoracic (4,0±0,8 pgPGI_2/mg/min) and abdominal (3,2±0,7 pg) aorta significantly more prostacyclin than in 5 control animals receiving the vehicle only (3,4 ± 0,6 pg and 2,3±0,7 pg) respectively. In 8 healthy males aged 26-32 years, a single intramuscular injection of 0,5 mg calcitonin led to an increase and measurable levels of 6-oxo-$PGF_{1\alpha}$ (about 100pg/ml) between 15 and 30 minutes after application (lower detection limit: 70 pg/ml). Calcitonin levels after 5 minutes increased to more than 1000pg/ml and started to decline after 60-120 minutes. In two healthy volunteers (physicians) 30 minutes after i.m. application of 0,5 mg calcitonin, PGI_2-formation in the forearm vein was examined by the bioassay technique of Moncada. The values after calcitonin application ($\bar{x}$ = 9,86 pg) were found to be enhanced in comparison to age and sex matched controls ($\bar{x}$ = 7,11 pg). The same 8 healthy males received also a depot-calcitonin and salmon-calcitonin (100 MRC-units), and the time course of 6-oxo-$PGF_{1\alpha}$ in unextracted plasma and caltitonin was was estimated. In 50 patients with peripheral vascular disease, after a single calcitonin administration,the 6-oxo-$PGF_{1\alpha}$ levels remained under the level of detection. It is discussed, whether the temporarily enhanced vascular PGI_2-synthesis as well as the increase of 6-oxo-$PGF_{1\alpha}$ -levels could be an explanation for the beneficial role of calcitonin seen in the treatment of this disease.