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EFFECT OF DIET AND CLOFIBRATE ON INCREASED PLATELET FUNCTION IN HYPERLIPOPROTEINEMIA. J.H. Joist, R.K. Baker, and G. Schonfeld. Departments of Medicine, Preventive Medicine and Pathology, Washington University School of Medicine, St. Louis, Missouri, U.S.A.

We have previously reported shortened template bleeding times (BT) in patients with type IIb and IV-hyperlipoproteinemia (HLP) and increased platelet coagulant activity (PF3a) in patients with types IIa, IIb and IV-HLP. We now report on a randomized, double-blind crossover study designed to assess the efficacy of lipid lowering diets appropriate for the respective type of HLP and Clofibrate versus placebo in reversing platelet hypersensitivity. 8 patients with IIa, 9 patients with IIb, and 9 patients with IV-HLP completed the study which included (a) baseline study (regular diet), (b) controlled diet (2 months), (c) controlled diet and Clofibrate (6 months), (d) controlled diet and placebo (6 months) (crossover design). In IIa-HLP patients the mean BT remained significantly shortened throughout all study periods whereas PF3a had reversed to normal at the end of the diet period without significant further changes thereafter. In IIb- and IV-HLP patients both shortened BT and increased PF3a observed at baseline normalized at the end of the diet period with a continuous further decline of PF3a thereafter regardless of Clofibrate or placebo. A small but significant decrease in total and LDL-cholesterol in serum was observed during the diet period in IIa-HLP patients and this decrease was not enhanced by Clofibrate. In IV-HLP patients, serum triglycerides had declined by 50% at the end of the diet period and stabilized at 25% of the initial value at the end of the first 6 month treatment period irrespective of Clofibrate or placebo treatment. No significant changes in triglyceride levels were observed in IIa- or IIb-HLP patients throughout the 14 month observation period. The findings indicate that lipid lowering diets may reverse platelet hypersensitivity in HLP patients and that Clofibrate has no effect on platelet function in HLP patients on a controlled lipid lowering diet.

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PLATELET NOREPINEPHRINE FLUXES IN NORMOTENSIVE SUBJECTS AND ESSENTIAL HYPERTENSIVE PATIENTS. C. Legrand, V. Dubernard and P. Meyer. Département de Néphrologie INSERM U7-CNRS LA 318 , Hôpital Necker, Paris, France.

Disturbed neuronal metabolism and storage of monoamines has been described in various experimental and human hypertensive diseases. Since blood platelets are considered as valid models of sympathetic neurons, the uptake and release of [^{3}H] norepinephrine (NE) was investigated in platelets isolated from normal subjects and from patients having essential hypertension. In addition, the intracellular metabolism of [^{3}H] -NE was followed by high performance liquid chromatography.

In basal conditions, NE was found to be slowly incorporated into the platelets and approximately 25% of the absorbed radioactivity was recovered as a sulfoconjugate metabolite which is thought to represent the cytoplasmic form of the monoamine. The uptake of NE was inhibited by drugs known to interfere with the platelet serotonin accumulation at the plasma membrane level (chlorimipramine, ouabain) or at the vesicular storage level(tyramine, reserpine). In addition, drugs which impair the intravesicular storage of monoamines leading to their accumulation in the cytoplasm, induced a marked increase in platelet NE metabolism and release.

The uptake of norepinephrine was slightly reduced in platelets from essential hypertensive patients. A marked increase in spontaneous NE release was measured in correlation with increased intracellular NE metabolism. The results are compatible with impaired intravesicular storage of the monoamine leading to increased diffusion through the plasma membrane.

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DECREASE OF PLATELET AGGREGATION IN RATS UNDER GASTRIC ULCER-CAUSING STRESS. T. Terano, T. Hamazaki, A. Hirai, Y. Tamura, and A. Kumagai. The 2nd Department of Internal Medicine, School of Medicine, Chiba University, Chiba, Japan.

Decreased platelet aggregability may play an important role in gastric ulcer continuation. We attempted to identify an antiaggregatory substance involved in stress induced gastric ulceration in rats. METHODS: 1) Male SD rats (180-220g) were stressed by water immersion, one group for 30 min and another for 120 min. Platelet rich plasma (PRP) and platelet poor plasma (PPP) were obtained from stressed rats and normal rats under ether anesthesia. Platelet aggregation was carried out by addition of 1/10 vol of 50μM ADP and was measured using a Sienco aggregometer. 2) Platelet-plasma mixing experiments. PRP from normal rats and from rats stressed for 30 min was centrifuged and the supernatant was discarded. Packed platelets from normal rats were resuspended in PPP from stressed rats and platelets from stressed rats were resuspended in PPP from normal rats. Also, platelets from each rat were resuspended in PPP of the same rat. Aggregation was then observed. 3) Stability tests of the activity in PPP from stressed rats which depressed platelet aggregation. PPP from normal and stressed rats was stored for 4 hr either in ice or at room temperature. Platelets from a normal rat were then mixed with each PPP. 4) 6 keto $PGF_{1\alpha}$ was measured by RIA. RESULTS: 1) The aggregability of rat platelets was decreased to 1/4-1/5 and to 1/10 of the normal value, after 30 min and 120 min stress, respectively. 2) Normal platelets suspended in PPP from stressed rats did not aggregate. Platelets from stressed rats suspended in normal PPP showed significant aggregability. 3) The antiaggregatory activity of PPP from stressed rats was lost significantly after storage at room temperature for 4 hr, while storage in ice did not greatly affect this activity. DISCUSSION: During water immersion stress which causes stomach ulceration of rats there appear platelet antiaggregatory substance(s) in plasma. Like PGI_2, the substance observed in this experiment is more stable at 0°C than at room temperature. However, plasma 6 keto $PGF_{1\alpha}$ concentrations in stressed rats did not increase enough to explain the decreased platelet aggregation. Identification of this antiaggregatory substance is now under way.

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POSITIVE AND NEGATIVE PLATELET AGGREGATION RESPONSES TO HUMAN TUMOR CELLS AMONG DIFFERENT NORMAL INDIVIDUALS. Antonio Ordinas, Eva Bastida, and G. A. Jamieson. Hospital Clínico y Provincial, Universidad de Barcelona, Spain, and American Red Cross, Bethesda, MD, USA.

Heparinized platelet-rich plasma from 16 normal donors has been examined for platelet aggregation in response to 6 cultured human tumor cell lines. All donors showed maximal aggregation equal to 10 μM ADP with U87MG (glioblastoma) with the exception of one donor (#7) who gave 50% response: donor 7 reacted with no other tumor cell line. With Hut 20 (large cell lung carcinoma, 10^5 cells/ml) six donors (#3, 4, 7, 14, 15 and 16) failed to show aggregation. With HT 29 (adenocarcinoma, 10^6 cells/ml), the same six donors (#3, 4, 7, 14, 15 and 16) plus three additional donors (#5, 9 and 10) failed to show aggregation with Hut 28 (mesothelioma) and SKNMC (neuroblastoma), the same nine donors (#3, 4, 5, 7, 9, 10, 14, 15 and 16) failed to show platelet aggregation at 5 x 10^6 cells/ml. None of the donors showed aggregation with the A549 line (epithelial lung carcinoma). Gel-filtered platelets show no aggregation response with any cell line. Crossover studies with responders and non-responders showed no differences in the platelets from different donors but did show that the aggregation response is dependent upon a plasma component. Interaction of platelets and tumor cells is thought to be an important factor in the metastatic dissemination of human cancer. Similar tumors are known to show different degrees of metastatic activity in different patients. The present results suggest that responders and non-responders may be identified from aggregation data and that this differentiation may depend on the presence of unidentified plasma factor(s).