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ASPIRIN AND THE KIDNEY IN PATIENTS WITH CEREBRAL ISCHEMIA.

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The acceptance of aspirin therapy for prevention of cerebral ischemia is based on positive results of several large clinical trials, and the usual dose is 1000-1500 mg/day. Several recent reports emphasize the adverse effects of aspirin and other nonsteroidal anti-inflamatory agents on renal function. We examined wether two extreme doses of aspirin (60 mg vs 1200 mg/day) could alter renal function in patients recently admitted to hospital with cerebral ischemia. We studied 33 patients with cerebral ischemia and no history of ingestion of aspirin nor other drugs two weeks prior to admission. During the first 5 days all patients received a 50 mEq sodium diet and no drugs, while during the second 5 days (trial) the patients were randomly assigned (double blind) to placebo, aspirin 20 mg or aspirin 400 mg, 3 times daily, with meals.

Overall, body weight increased by 650 g in patients taking 1400 mg/day of aspirin ($p < 0,01$), but not in patients taking 60 mg/day. Also increases in systolic and diastolic blood pressure did not reach significant differences. While waiting more reports, aspirin at doses near 1000 mg should be administered cautiously in sodium restricted patients with cerebral ischemia. Acute water retention may be specially troublesome.

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CYCLOOXYGENASE INDIPENDENT PLATELET AGGREGATION:RELATION WITH ASPIRIN CONCENTRATION.

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Low doses of aspirin (20 mg/day) were previously reported to be uneffective in preventing platelet aggregation (PA) induced by pairs of aggregating agents such as PAF and adrenalin.This was in part attributed to the inability of such treatment to inhibit lipooxygenase-dependent PA.The latter can be observed in vitro in"aspirinated"platelets stimulated with high quantities of aggregating agents.The aim of this study was to evaluate if the lipooxygenase-dependent PA was influenced by aspirin in a dose-dependent fashion. PA was studied in platelet rich plasma (PRP)(Born's method) by using threshold doses of aggregating agents (TDA) such as PAF(4-75 nM),epinephrine(0.6-2 μM) and collagen(2-4 μg/ml).PA performed in PRP pretrated with 100 μM aspirin was fully prevented;in the same samples thromboxane (Tx) A_2 evaluated by its metabolite Tx B_2 was almost absent.Increasing amount of PAF(20 fold TDA),epinephrine(20 fold TDA) and collagen (36 fold TDA) do aggregate"aspirinated"platelets;similarly"aspirinated"platelets aggregate when stimulated with a pair of aggregating agents (TDA of PAF+epinephrine).This phenomenon was not detected if platelets were incubated with higher amounts of aspirin (250-500 μM).The study suggests that aspirin could influence lipooxygenase-dependent PA.This hypothesis is supported by a research showing the aspirin inhibits dose-dependently platelet HETE formation.A further study is now in progress to evaluate the influence of high doses of aspirin on cyclooxygenase-independent PA in vivo.

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LIPOXYGENASE PRODUCTS CHANGES IN 'IN VITRO' AND 'IN VIVO' ASPIRINISED PLATELETS UNDER THE INFLUENCE OF PAF AND EPINEPHRINE

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We aimed to investigate the changes of lipoxygenase products in platelets and the simultaneous behaviour of 'in vivo' or 'in vitro' aspirinised platelets, stimulated by two agonists, PAF and epinephrine (EPI). 12 healthy were included. 6 received 20mg of aspirin (ASA) per os for 7 days (group A), and in 6 (group B) platelets were aspirinised 'in vitro' (5 or 10min incubation at 37°C with ASA 1M). In group A blood was drawn once at the beginning and once at the end of the trial, while in group B just once. First, platelet aggregation was studied using two agonists simultaneously (0.6 μM EPI and 20 nM PAF). We incubated then all platelet samples with 0.5 M of the substance BW755C (kind offer of Dr Moncada) for 3 min at 37°C. Second we measured PLO products according to Takayama et al (1980), in platelets with or without ASA, and in platelets with ASA and after treatment with BW755C, always after addition of both agonists. Our results showed: a) Irreversible aggregation was slightly enhanced by the simultaneous addition of PAF and EPI in both groups and in non-aspirinised platelets. After ASA treatment, each agonist alone did not induce irreversible aggregation, whereas their combination overcame this inhibition, a fact not noticed under BW755C (a known PLO inhibitor). b) PLO products were measured in nmol TBRS/10^9 platelets:

	PRIME	ASA	ASA+BW755C
A ($\bar{X}$+SD)	1.44+0.37	1.70+0.44	0.80+0.30
B ($\bar{X}$+SD)	1.32+0.33	1.34+0.29	0.27+0.07

Our results agree with Cerletti et al (1986) and confirm that the two agonists combined are capable of overcoming the inhibition caused by ASA, possibly by activating the PLO pathway (Cerletti et al, 1986). Respectively the quantitative determination of PLO products (about which we did not notice any other report insofar) confirm the above assumption, since inhibition by BW755C coincides with the steep fall of PLO levels, which for group A is statistically significant ($p < 0.01$, paired t-test) and for group B entirely significant ($p < 0.001$).

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INFLUENCE OF CELL CYCLING ON MAGNITUDE OF RESPONSE OF HUMAN UMBILICAL VEIN ENDOTHELIAL CELLS (EC) TO NOREPINEPHRINE (NE) AND HISTAMINE (H).

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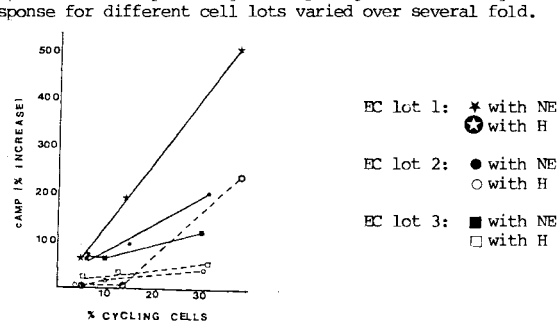
EC have several roles in preventing thrombosis. Efficiency with which EC fulfill these might well influence outcome of potentially thrombotic stimuli. Thus, factors that influence EC function are of interest. As a general measure of EC response to NE and H the level of cAMP was measured. EC were harvested and passaged by enzymatic digestion and grown in DMEM plus 10% fetal calf serum and antibiotics. cAMP was assayed by radioimmunoassay. Percentage cycling cells was determined by autoradiography of cultures pulse labeled with tritiated thymidine and was increased by hydroxyurea treatment.

Basal cAMP was remarkably consistent (less than 10% difference) for cells isolated from different cords, studied after different number of passages, fresh or frozen and with varying percentage of cells cycling. However, magnitude of response to agonists was highly variable. Within the same cell lot between 5-8 passages, magnitude of response was directly proportional to percentage of cycling cells but magnitude of response for different cell lots varied over several fold.



EC response to NE was mediated through B-adrenergic receptors and that to H through H^2 receptors. Variability might be caused by differences in receptor number or some intracellular process.