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Title : PLATELET AGGREGATION IN MALIGNANT HYPERPYREXIA PATIENTS

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The laboratory diagnosis of Malignant Hyperpyrexia(MH) is at present most reliably made by assessing the in vitro contracture response of biopsied skeletal muscle to caffeine and halothane. A less invasive technique would be of great clinical value.

Platelets resemble skeletal muscle in that they contain actin and myosin filaments, ATPases under Ca^{++} control, as well as proteins that are similar to tropomyosin.[1] Interestingly, a coagulopathy may accompany an episode of MH. Thus, it has been suggested that platelet physiology might be abnormal in MH patients. Indeed Zsigmond et al.[2] noted that epinephrine-induced second wave platelet aggregation was lacking in patients at risk to develop MH.

We, therefore, attempted to further define the usefulness of platelet studies in the diagnosis of MH.

Methods. Five patients with muscle biopsy proven MH (3 had clinical episodes of MH) were studied. The patients abstained from aspirin-containing medication for 2 weeks. Platelet-rich plasma(PRP) was prepared as described previously.[3] Platelet aggregation was determined by light transmission, and was induced by either ADP or epinephrine.[3] Since a defect in second wave aggregation must be accompanied by altered platelet granule release,3 serotonin release was also evaluated by incubating platelets with ^{14}C serotonin and measuring the amount released after aggregation by scintillation technique.[4]

Diagnosis of MH susceptibility by muscle biospy was made utilizing rectus or quadriceps muscle strips incubated at 37°C. Solutions were continuously bubbled with 95% O_2-5% CO_2 in human Krebs Ringer's solution. Contracture response to halothane alone and incremental doses of caffeine (0.25 mM-16 mM) were measured. MH was diagnosed if contracture greater than 0.4 gm was observed in the presence of <2% halothane alone or contracture greater than 0.1 gm in the presence of 1 mM caffeine or greater than 0.3 gm in the presence of 2 mM caffeine.

Results. Normal second wave platelet aggregation was observed in all patients (Table & Figure) when platelets were challenged with either ADP or epinephrine. Furthermore, release of ^{14}C serotonin was unimpaired in all cases. Platelets from one patient, a 22 year-old male who survived MH, demonstrated marked hypersensitivity to epinephrine.

Discussion. This study clearly demonstrates that platelets from MH susceptibles respond appropriately to soluble aggregating agents. Second wave aggregation is always seen and release of granule contents proceeds unimpaired. It is difficult to reconcile this data with those previously reported[2] since even incipient aspirin effect is not consistent with the proposed platelet functional defect.

Interestingly, one individual showed a marked hypersensitivity to epinephrine, which is seen in some patients with diabetes and hyperlipidemia. Based on this individual, further studies to define the relationship between altered platelet function and MH are desirable. Altered platelet reactivity in the form of defective second wave aggregation and release of granule contents, however, is certainly not present in this group of MH patients.

References.

1. Lüscher EF: Microfilaments in Blood Platelets, Molecular Basis of Motility. Edited by Heilmeyer LMG, Jr., Rüegg JC, and Wieland Th, N.Y., Springer-Verlag, 1976, pp 175-185

2. Zsigmond EK, Penner J, Kothary S: Normal Erythrocyte Fragility and Abnormal Platelet Aggregation in MH Families: A Pilot Study, Second International Symposium on Malignant Hyperthermia. Edited by Aldrete JA and Britt BA. N.Y., Grune & Stratton, 1977, pp 213-220

3. Addonizio VP, Edmunds LH, Colman RW: J Lab Clin Med 91:989-997, 1978

4. Jerushalmy Z, Zucker MB: Thromb Diath. Haemorrh 15:413, 1966

TABLE I: Second wave aggregation in MH patients.

Patient	Age	Sex	EPINEPHRINE: uM epi for 2nd wave aggregation	EPINEPHRINE: % Aggregation	EPINEPHRINE: % Release ^{14}C Serotonin	ADP: uM ADP required for 2nd wave aggregation	ADP: % Aggregation	ADP: % Release ^{14}C Serotonin
1.	30	M	2.5	67.50	47.85	5.0	70.00	46.19
2.	19	M	2.5	68.75	50.00	5.0	65.00	26.80
3.	22	M	0.025	87.50	51.37	0.5	76.25	58.73
4.	24	F	1.0	75.00	40.90	2.0	82.50	21.90
5.	32	M	1.0	78.75	61.30	5.0	78.75	53.50
Normal Range:			1-5	>56%	25.0-84.0	0.05-5.0	>62%	19.6-75.2

Figure: Normal first and second wave aggregation in patient #2 induced by 2.5 μM epinephrine.