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Inhibition of aggregation and plug formation of platelets subjected to ultrasound and tested in the revolving plastic loop

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Treatment of platelet-rich plasma (PRP) with low intensity ultrasonic energy initiates platelet aggregation. This aggregation might be caused by release of adenosine diphosphate or 5-hydroxytryptamine from the treated platelets and is inhibited by substances which stabilize membranes (Michal, 1970). These experiments were carried out in the aggregometer (Born, 1962). It was considered of interest to study the effects in another test system for measuring platelet aggregation.

The method of Silver (1970) was used. PRP is rotated in a plastic loop and four parameters of aggregation are observed in the following sequence: first visible particles, 'snow storm', large aggregates, platelet plug. These parameters indicate an increasing degree of aggregation.

Human, citrated PRP at room temperature was oscillated at 20 KHz and very low energy levels by dipping a needle probe of the ultrasonic transducer below the surface. The energy levels (1–5 J) were considerably lower than those which would cause gross damage to the platelets. The PRP was then transferred to the loop, rotation started and the onset of each of the aggregation parameters was noted.

There was a direct relationship between the amount of energy applied to the sample of PRP and the degree of aggregation observed. The amount of energy required to produce a specific aggregation parameter varied from one subject's plasma to another.

Amitriptyline, added to the PRP before the energy was applied, inhibited plug formation at final concentrations between 10^{-8} and 10^{-5} M depending on the particular plasma and on the intensity of energy used to initiate aggregation. The inhibition of the other parameters of aggregation depended on the concentration of amitriptyline.

This system would appear to be a sensitive method for measuring the effects of drugs on platelet aggregation and plug formation.

REFERENCES

BORN, G. V. R. (1962). Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature, Lond.*, **194**, 927–929.

MICHAL, F. (1970). Platelet aggregation by very low intensity acoustical energy and its inhibition by drugs. *Br. J. Pharmac.*, **40**, 544*P*.

SILVER, M. J. (1970). Platelet aggregation and plug formation: a model test system. *Am. J. Physiol.*, **218**, 384–388.

Renal handling of Paraquat

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Paraquat (PQ) is a widely used herbicide, with the systematic name 1,1′-dimethyl-4,4′-dipyridylium dichloride. Experiments with animals have shown that it exists as the cation at physiological pH and that there is no appreciable degree of binding to plasma proteins (Daniel, personal communication).

We have been examining the renal handling of PQ, using adult male beagle dogs (Alderley Park strain) anaesthetized with pentobarbitone (30 mg/kg i.v.). In clearance studies, PQ was infused intravenously with inulin and *p*-aminohippurate (PAH) during water, saline or mannitol diuresis. Urine and plasma samples were analysed for PQ, inulin, PAH, urea, osmolality, sodium, potassium, calcium and magnesium, and the respective clearances calculated.

Initial experiments showed that there was net reabsorption of PQ in the kidney, the percentage reabsorption of filtered PQ varying from 35 to 65%. The PQ clearance was independent of plasma concentration over the range 10–150 μg/ml and, in most experiments, varied directly with urine flow. Ratios of the concentration of urine to plasma were never less than unity, but could approach this value at high urine flow rates, suggesting that passive diffusion was responsible for the reabsorption.

Further evidence against an active process for PQ reabsorption derives from experiments with diuretics (ethacrynic acid and mersalyl), where the increased clearance of PQ may be explained by postulating that the rate of diffusion of PQ may be decreased by other solutes, for example electrolytes (Giotti & Maynert, 1951). In two experiments, however, the substitution of *iso*-osmotic NaCl solutions for hypertonic mannitol infusions, which reduced urine flow and total solute output, unexpectedly increased the percentage excretion of PQ. These results are unexplained.

In an attempt to localize the site of PQ reabsorption, stop-flow experiments were carried out according to the technique of Malvin, Wilde & Sullivan (1958). The results indicated that PQ is reabsorbed in the proximal half of the nephron. There was no indication of any secretory component. The parallel rise in PQ concentration and urine osmolarity seen in distal samples suggests that this tubule segment is relatively impermeable to PQ.

Thus we conclude that PQ is reabsorbed in substantial quantities in the dog kidney, and this reabsorption probably occurs in the proximal tubules and that, while conclusive proof has not been presented to eliminate an active reabsorptive component, most results can be adequately explained by passive diffusion.

REFERENCES

GIOTTI, A. & MAYNERT, E. W. (1951). The renal clearance of barbital and the mechanism of its reabsorption. *J. Pharmac. exp. Ther.*, **101**, 296–309.

MALVIN, R. L., WILDE, W. S. & SULLIVAN, L. P. (1958). Localization of nephron transport by stop flow analysis. *Am. J. Physiol.*, **194**, 135–142.