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0202 PROSTACYCLIN AND THE MECHANISM OF ACTION OF ANTITHROMBOTIC DRUGS

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The balance between the proaggregating thromboxane A_2 and the anti-aggregating prostacyclin forms a homeostatic mechanism for the control of platelet aggregability in vivo. Prostacyclin is a circulating substance released from the lungs which acts by stimulating adenylate cyclase leading to an increase of cyclic AMP in the platelets. The mechanism of antithrombotic action of phosphodiesterase inhibitors like dipyridamole depends on their ability to potentiate the effect of endogenous PGI_2. Prostacyclin and TXA_2 are inhibited by aspirin but the enzyme which synthesises TXA_2 is more sensitive to the inhibitory effect of aspirin, therefore it is possible to administer doses of aspirin which by inhibiting selectively TXA_2 will have an antithrombotic effect. Human studies demonstrate that cutaneous bleeding time is controlled by the balance between TXA_2 and PGI_2 and can be manipulated by using different doses of aspirin.

0203 A CLASS OF DRUGS THAT INHIBITS PLATELET RELEASE AND AGGREGATION BY APPARENT INTERFERENCE WITH ANION TRANSPORT

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The platelet release reaction is analogous to the process of exocytosis by which many other secretory cells release hormones or mediators from intracellular granules. Anion transport blocking (ATB) drugs inhibit release of epinephrine from isolated chromaffin granules (CG) by blocking chloride uptake and preventing osmotic lysis. Studies on platelets analagous to those done on CG showed that increasing osmotic strength in the range 600-1000 mOsm progressively suppressed serotonin release to completion and that ATB drugs (viz. probenecid, SITS, pyridoxal phosphate and suramin) at mM concentrations completely inhibited release and aggregation of human platelets stimulated by thrombin, ADP, A23187, epinephrine or collagen. Sulfinpyrazone has the appropriate structure for anionic blocking, and may suppress platelet function as effectively by this mechanism as by cycloxygenase inhibition. The ATB drugs acted apparently to prevent movement of OH^- from the more alkaline medium into the relatively acidic granule, for platelet release was not inhibited by replacing anions with isethionate or sucrose, but was markedly dependent on OH^- in the pH range 6 to 7.5 where inhibition by the ATB drugs was competitive with respect to OH^-. Since the ATB compounds include some relatively nontoxic drugs in common use, and since their action on platelets differs markedly from that of aspirin, they should receive attention as potential alternative or auxillary antithrombotic agents.