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Prostaglandin E_1 itself is one of the most potent pharmacologically active substances known, and we plan to investigate in detail the potential of these more active synthetic compounds. It is also hoped that with an extended pharmacological profile of various synthetic isomers of the parent prostaglandin structures as they become available, compounds which show but one facet of the wide spectrum of activity presently associated with the prostaglandin class of compounds will be obtained.

We thank Sheila Jessup and Wendy McDonald-Gibson for assistance. This work was supported by grants from the US National Institutes of Health to Harvard University and by grants to the Worcester Foundation for Experimental Biology. Prostaglandin E_1, $F_{1\alpha}$ and 15-*epi* prostaglandin E_1 were supplied by Drs J. Pike and W. P. Schneider, the Upjohn Company, and Dr B. Samuelsson, Stockholm.

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Received December 31, 1968.

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D-Receptor for Serotonin on Blood Platelets

Blood platelets contain a high concentration of 5-hydroxytryptamine or serotonin[1] which they accumulate from the surrounding medium against high concentration gradients by an active transport mechanism[2-4]. The addition of 5-hydroxytryptamine (5-HT) to blood causes the blood cells including platelets to form clumps[5] and in stirred plasma rich in platelets the aggregation of platelets in response to added 5-HT is dependent on concentration[6-8]. It has been suggested that all aggregators of platelets, including 5-HT, clump platelets by releasing the platelet adenosine diphosphate[9,10]. Recently, Baumgartner and Born concluded that blood platelets contain on their membranes receptor sites specific for 5-HT and that these receptor sites are involved with both platelet aggregation and the active uptake of the amine by the cells[8]. The work reported here suggests that the receptors strongly resemble the classical D-receptors for 5-HT on the smooth muscle of the intestine.

Platelet aggregation was studied by the turbidimetric method similar to that originally described by Born[11] and modified to record changes in optical density of plasma rich in platelets in response to aggregating agents on a potentiometric recorder[12,13]. Plasma rich in platelets was prepared from sheep blood using trisodium citrate (final concentration of 0·38 per cent) as previously described[12,14] and all experiments were carried out at 37° C. Drugs were added by microsyringes to the accurately stirred 3 ml. samples of plasma, rich in platelets, in volumes not exceeding 0·05 ml.

The addition of 5-HT to stirred, citrated plasma rich in platelets produced an immediate and, in low concentrations, a reversible aggregation of the platelets. As a result of this the optical density of the platelet suspension was reduced and the change was found to be linearly related to the concentration of 5-HT added (Fig. 1). As is the case with ADP[15] or the more potent aggregator, 2-chloroadenosine diphosphate[12], the onset of aggregation was quite rapid, and quantitative assessment of platelet cohesion and its inhibition could be obtained by measuring the initial rates of aggregation (slopes/first 30 s). The rates of aggregation increased in a linear fashion with the logarithm of the concentration of 5-HT added up to a final value of 8 to 10 μM of the aggregator. Concentrations in excess of this amount resulted in a progressive diminution of the response. These observations are in agreement with similar findings by Baumgartner and Born[8].

It has been proposed that the 5-hydroxytryptamine receptors on the smooth muscle of the guinea-pig ileum are of two kinds: those blocked by dibenzyline, dihydroergotamine and lysergic acid diethylamide (the D type receptors) and those susceptible to atropine, morphine and cocaine (the M type receptors), and that biological systems responsive to 5-HT may contain these receptors in varying degrees[16]. Minute concentrations of lysergic acid diethylamide (LSD-25) inhibited platelet aggregation induced by 5-HT; a 3 nM concentration was sufficient to reduce platelet response to 2 μM 5-HT by 50 per cent (Fig. 2). The antagonism was dependent on concentration, and the effectiveness of LSD-25 increased with the time of contact with the platelets. Incubation of LSD-25 in plasma rich in platelets for 10 min before the addition of the aggregator produced its optimal effect as an antagonist of platelet clumping caused by 5-HT. Aggregation of platelets induced by ADP was not influenced significantly by concentrations of LSD-25 in excess of 1,000 μM (Table 1). This great selectivity suggests that LSD-25 interferes specifically with the platelet 5-HT receptor and that it does not affect the ability of platelets to aggregate in the presence of added ADP. It is interesting to note also that Gaddum[17] found the pA_2 value for LSD-25 with 10 min contact period to be in the order of 8·7 for the antagonism of contractions of the rat uterus induced by 5-HT. This compares favourably with the value of 8·5 obtained by allowing LSD-25 to remain in contact with platelets in plasma rich in platelets for 10 min before the aggregator (5-HT) was added. The other D type receptor blocker

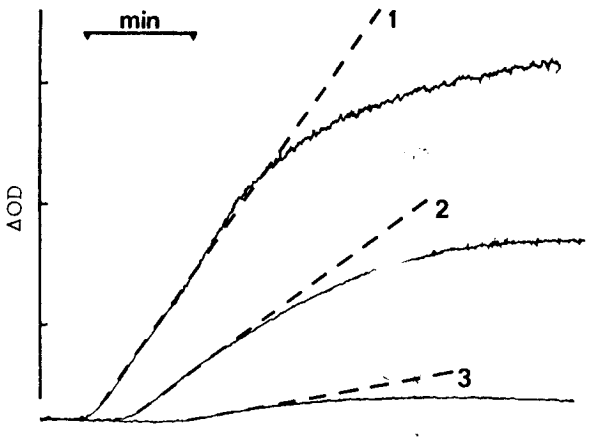

Fig. 1. Aggregation of blood platelets in stirred plasma rich in platelets from sheep in response to added 5-hydroxytryptamine. The initial rate of change in the optical density (Δ OD, arbitrary units) is represented by the interrupted lines. Concentrations of 5-HT used were: (1) = 2 μM; (2) = 1 μM; (3) = 0·5 μM.

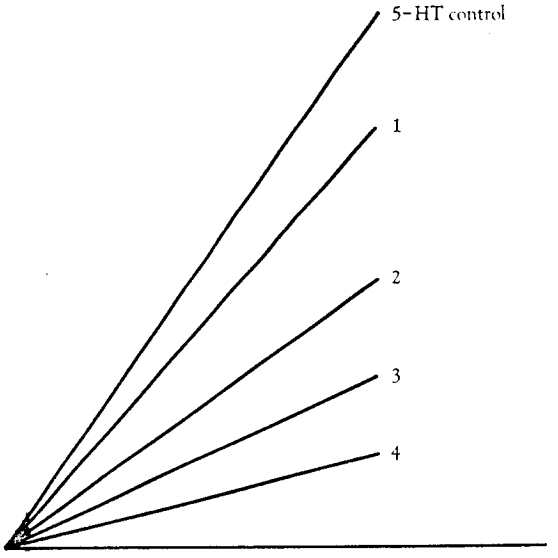

Fig. 2. Graphical representation of the initial rates of platelet aggregation in stirred plasma rich in platelets induced by 5-HT (2 μM) alone, and in the presence of lysergic acid diethylamide in concentrations of 1 nM (1); 3 nM (2); 6 nM (3); and 12 nM (4). Slopes were obtained by drawing tangents to the steepest portion of the aggregation response curves during the first 30 s.

used, dibenzyline, was also found to be a potent and selective inhibitor of platelet clumping caused by 5-HT and to be without appreciable activity against platelet clumping induced by ADP. The blockers of intestinal M receptors for 5-HT, morphine and cocaine, affected neither the aggregation of platelets induced by 5-HT nor the clumping caused by ADP at concentrations exceeding 1,000 μM. In addition, these substances did not potentiate the effect or add to the inhibitory activity of LSD-25 or dibenzyline in a synergistic manner. Atropine was the only M type blocker which antagonized 5-HT clumping of platelets, but its effect was apparent only at a concentration of 3·4 μM or approximately one thousand times greater than the concentration of LSD-25 required for similar antagonism. It therefore appears that the platelet receptors for 5-HT are predominantly sensitive to the D type serotonin inhibitors.

Table 1. INHIBITION OF PLATELET AGGREGATION INDUCED BY 5-HT AND ADP IN THE PRESENCE OF SEROTONIN ANTAGONISTS OF D AND M RECEPTOR SITES

Antagonist concentration (μM) needed for 50 per cent inhibition of clumping*

	Platelet clumping induced by 5-HT (2·0 μM)	Platelet clumping induced by ADP (1·5 μM)
LSD-25	0·003	> 1,000
Dibenzyline	0·008	> 1,000
Atropine	3·4	> 1,000
Morphine	> 1,000	> 1,000
Cocaine	> 1,000	> 1,000

* Averages of six or more experiments.

The blood platelet membrane is very similar to the membrane of the smooth muscle cells. By the use of selective adrenolytic agents it has been demonstrated that platelets contain alpha adrenergic receptors[18,19]. Born and his colleagues[20] and our own studies (F. M. and R. H. Thorp, results to be published) indicate that adenosine and its analogues which inhibit platelet aggregation *in vitro* are also effective vasodilators *in vitro*. Furthermore, it has been demonstrated that ADP acts at a specific receptor site on the platelet membrane where it can be antagonized by adenosine in a competitive manner[12,21,22]. The number of such receptor sites has been assessed to be approximately 10^5 per platelet[21,23]. Receptors specific for 5-hydroxytryptamine on the platelet membrane have recently been postulated, numbering about 10^4 per platelet, and it has been suggested that these receptors are responsible for the aggregation response of platelets exposed to 5-HT *in vitro*[6]. The experiments described here suggest that the platelet 5-HT receptors are of the classical D type, not unlike those involved in the response of the guinea-pig ileum to 5-hydroxytryptamine. The demonstration that the response of the platelets to 5-HT can be inhibited by agents which antagonize the action of serotonin on plain musculature may be of clinical as well as of fundamentally pharmacological interest. The therapeutic use of drugs with D-type blocking activity may affect the rate of uptake of 5-HT by the blood platelets and their sensitivity to the amine. The changed responsiveness of platelets may in turn have a significant effect on their function in haemostasis and thrombosis[6,7].

I thank Professor R. H. Thorp for his interest.

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Received November 5, 1968; revised January 27, 1969.

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Deposition of Aerosol Particles in the Nasopharyngeal Region of the Human Respiratory Tract

THE interest of those concerned in any way with the provision of protection against inhalation hazards, especially those associated with work with radioactive materials, has been stimulated by the publication of the report of the Task Group on Lung Dynamics for Committee II of the International Commission on Radiological Protection[1]. Investigations in the Health Physics and Medical Division at AERE, Harwell, into the behaviour of inhaled radioactive aerosol particles in the human respiratory tract have started—with the cooperation of three volunteer subjects—with a study of deposition in the nasopharyngeal compartment. The experiments followed the somewhat artificial procedure of earlier investigators and aerosols were drawn through the nose and mouth at flow rates of 5, 10, 20, 30 and 40 l./min while the subject held his breath.

Monodisperse particles of polystyrene ($\rho = 1{\cdot}2$), diameter 1·6–7·3 μm and labelled with ^{82}Br, were used. Small volumes (0·1 ml.) of suspensions of these particles in alcohol were atomized in about 1 s to give a cloud of dry particles which was used as the test aerosol. The aerosol