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Time-dependent potentiation and inhibition by 5-hydroxytryptamine of platelet aggregation induced by ADP

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Platelet aggregation by adenosine diphosphate (ADP) can be either potentiated or, under certain conditions, inhibited by 5-hydroxytryptamine (5-HT) (Baumgartner & Born, 1968). We have investigated these opposing effects. Platelet aggregation was measured in human citrated platelet-rich plasma by the photometric method (Born, 1962). The uptake of 5-HT into platelets was measured with 5-HT labelled with ^{14}C.

In the presence of 5-HT, platelet aggregation by ADP was first accelerated and then decelerated (Figure 1). The acceleration was greatest when 5-HT and ADP were added simultaneously. With increasing intervals between the addition of 5-HT and the subsequent addition of ADP, the potentiation disappeared and was followed by inhibition. The inhibition increased for 10 min and then decreased; after 30 min the aggregation velocity was again similar to that of controls.

Earlier work (Born, Juengjaroen & Michal, 1972) showed that platelet aggregation by 5-HT is inhibited strongly by methysergide ($K_i \approx 0.03\ \mu M$) and weakly by imipramine ($K_i \approx 10\ \mu M$) whereas the uptake of 5-HT by platelets is inhibited strongly by imipramine ($K_i \approx 0.3\ \mu M$) and weakly by methysergide ($K_i \approx 125\ \mu M$). Methysergide at 0.25 μM completely inhibited both potentiation and inhibition by 5-HT of aggregation by ADP. Imipramine at 0.5 μM, and also at 5 μM which inhibited 5-HT uptake completely, only partially prevented the potentiation but did not prevent the inhibition nor the subsequent recovery. Ouabain at up to 100 μM influenced neither potentiation nor inhibition.

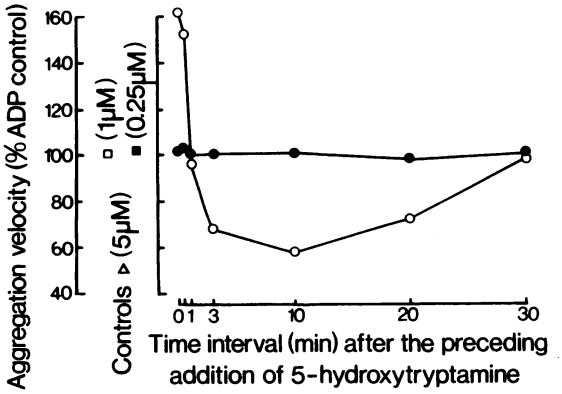

Figure 1 Aggregation velocity of human platelets (expressed as percentage of ADP control) produced by 1 μM ADP at different intervals after preceding addition of 5 μM 5-HT in the presence (●) and the absence (○) of 0.25 μM methysergide (MeS). For comparison aggregation velocities of 5-HT (△) and ADP alone (□) and ADP in the presence of methysergide (■) are indicated on the left of the figure. Methysergide was added 5 min before 5-HT or ADP; all samples were incubated for 30 min at 37° C before the addition of the aggregating agent.

Further evidence that both potentiation and inhibition of aggregation velocity by 5-HT are independent of the uptake of 5-HT was obtained with 5-methoxy-α-methyltryptamine (5 μM) which is not taken up by platelets (Born *et al.*, 1972) yet produced both potentiation and inhibition just like 5-HT itself. Therefore these effects of 5-HT are unrelated to its uptake by platelets but rather to a reversible effect of 5-HT on the plasma membrane.

M. Motamed is in receipt of a fellowship from the Wellcome Trust. F. Michal is a Senior Research Fellow of the British Heart Foundation.

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The effect of histamine on tissue blood flow in the cat

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Histamine lowers blood pressure in the cat by causing vasodilatation. This response involves histamine H_1- and H_2-receptors (Owen & Parsons, 1974; Flynn & Owen, 1974). The experiments described in this communication were designed to help our understanding of the distribution of histamine receptors through the peripheral circulation.

Experiments have been made in cats, body weight 1.2-2 kg, anaesthetized by an intraperitoneal injection of chloralose 40 mg/kg and urethane 600 mg/kg. The trachea was cannulated. Blood pressure was measured from the right brachial artery. Histamine was infused via the right brachial vein. Heart rate was measured from the blood pressure pulse. Cardiac output and tissue blood flows were measured using radioactive microspheres, 25 μ diameter (3M Company). Detailed accounts of the microsphere technique and validation of its principles have been described elsewhere (Rudolph & Heymann, 1967; Neutze, Wyler & Rudolph, 1968; Wagner, Rhodes, Sasaki & Ryan, 1969; Warren & Ledingham, 1974).

Two injections of microspheres, about 100,000 spheres per injection, were made in each experiment. During a control period microspheres labelled with ^{46}Sc were injected. Infusions of histamine (10, 33 or 100 nmol kg^{-1} min^{-1}) or saline (control experiments) were then started. The second injection of microspheres, labelled with ^{85}Sr, was made during the continued infusion, 30 min after the start of the infusion.

Histamine caused dose-dependent falls in blood pressure, but did not change heart rate or cardiac

Table 1 Effect of histamine on blood pressure and tissue blood flow

Histamine infusion nmol kg^{-1} min^{-1}	0 (saline infusions)	10	33	100
	n = 8	n = 6	n = 6	n = 6
Mean blood pressure mm Hg				
Before infusion	119.3 ± 6.5	132.3 ± 8.6	135.3 ± 8.4	113.3 ± 5.8
During infusion	108.8 ± 5.9	120.3 ± 8.4	109.8 ± 3.5	66.5 ± 2.7
		Blood flow ml min^{-1} 100 g^{-1} ± s.e.m.		
Brain	63.1 ± 6.0	72.2 ± 5.7	66.5 ± 10.2	40.5 ± 4.6
Heart	281.3 ± 32.2	361.6 ± 43.1	593.7 ± 61.5	655.6 ± 53.4
Kidneys	346.8 ± 32.5	316.2 ± 36.1	409.2 ± 37.6	238.5 ± 23.5
Stomach	17.3 ± 2.2	22.7 ± 3.2	40.1 ± 6.4	94.1 ± 18.6
Small intestine	34.8 ± 4.3	35.3 ± 3.0	44.5 ± 4.9	36.9 ± 10.2
Large intestine	50.6 ± 8.9	57.9 ± 5.6	64.1 ± 14.5	53.7 ± 11.4
*Liver	97.1 ± 8.2	109.8 ± 14.4	103.8 ± 15.2	54.2 ± 4.2
Adrenal glands	469.4 ± 81.8	444.1 ± 66.7	546.9 ± 267.8	379.5 ± 56.0
Skeletal muscle	4.4 ± 0.8	3.9 ± 0.9	3.7 ± 1.0	2.8 ± 0.3
Skin	3.5 ± 0.7	4.8 ± 0.7	3.1 ± 0.6	1.4 ± 0.2

All values from the second injection of microspheres during infusions.
The pre-infusion blood flows in all groups were not significantly different from the values shown during the infusions of saline.
* Excludes portal blood flow.