present being evaluated as antithrombotic agents (Elwood, Cochrane, Burr, Sweetnam, Williams, Welsby, Hughes & Renten, 1974), this may be of considerable physiological importance.

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Transport of 5-hydroxytryptamine by rat and human platelets

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Blood platelets transport 5-hydroxytryptamine (5-HT) from the plasma and store it in granules as a macromolecular complex with ATP and calcium (Born & Gillson, 1959; Da Prada & Pletscher, 1968). This transport process is similar to that of serotonergic neurones, and for this reason platelets have been used with some success as models of aminergic neurones (Sneddon, 1973), particularly for investigating the effects of drugs on 5-HT uptake. Most investigations of 5-HT uptake by platelets have used human platelet-rich plasma (PRP), and as much of the experimental work on serotonergic neurones has been carried out in rats we wished to compare the characteristics of 5-HT transport by rat and human platelets.

Uptake of 5-HT by rat platelets was measured as described by Drummond & Gordon (1976), and the same technique was used for studies with human PRP. The initial rate of 5-HT was much faster in rat than in human PRP, and at submicromolar substrate concentrations the linear component of uptake in both species lasted for at most 10 seconds. In rat PRP, 5-HT uptake was so rapid that substrate depletion (with consequent limitation of uptake) occurred within 60 s, but this could be greatly reduced by diluting the PRP with cell-free plasma, to lower the platelet count from its normal value of 10^9 cells/ml to about 2×10^8 cells/ml (comparable with the platelet count in human PRP). Lineweaver-Burk analysis of uptake after 10 s incubation of PRP with 5-HT (0.3–2.5 μM) gave apparent K_m values of 1.0 μM for human platelets and 0.75 μM for rat. Values for V_{max} were 20 pmol 10^8 cells^{-1} 10 s^{-1} for human platelets and 60 pmol 10^8 cells^{-1} 10 s^{-1} for rat.

Uptake of 5-HT by both rat and human platelet was extremely temperature sensitive over the temperature range 17–37°C. At lower temperatures, human platelets transported very little 5-HT, whereas rat platelets apparently retained the ability to transport significant amounts at temperatures as low as 7°C. Since this transport by rat platelets at low temperatures was not inhibited by chlorimipramine, however, it seems likely that it represents facilitated diffusion rather than active uptake.

Tricyclic antidepressants, which are believed to exert their clinical effects partly by inhibiting 5-HT transport in serotonergic neurones, are also competitive inhibitors of platelet 5-HT uptake. In some studies, however, these compounds have been tested by incubating 5-HT in PRP for 1 min or more (Buczko, De Gaetano & Garattini, 1975; Horng & Wong, 1976), and because uptake then is much slower than the initial rate (especially in rat PRP) the potency of competitive inhibitors may be underestimated. For example, when we measured the uptake of 0.8 μM 5-HT by rat PRP after 10 s incubation at 37°C, the IC_{50} value for chlorimipramine was 0.1 μM, but when this experiment was repeated, incubating the 5-HT in PRP for 3 min, the IC_{50} value for chlorimipramine was 2.0 μM.

Uptake of 5-HT by rat platelets is inhibited by ADP (Drummond & Gordon, 1976). We found that ADP was a less potent inhibitor in human than in rat PRP, when uptake was measured after 10 s incubation of 5-

HT in PRP, but when 5-HT was incubated in human PRP for 1 min or longer, the inhibitory effect of ADP was increased. The mechanism by which ADP inhibits 5-HT uptake is not fully understood, but since it occurs at submicromolar concentrations of ADP, it may be of considerable physiological significance.

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A further action of sodium cromoglycate

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At the last meeting of the British Pharmacological Society at Chelsea College we described a model of reflex bronchoconstriction in the anaesthetized dog (Richards & Jackson, 1976). The activity of sodium cromoglycate (DSCG) has now been investigated using this model.

Beagle dogs of either sex and weighing 9–12 kg were used in this study. The dogs were initially sedated with thiopentone sodium (5–10 mg/kg i.v.) and then anaesthetized with chloralose (80 mg/kg i.v.). The dogs were respired at constant pressure with a Bird Mk. VII ventilator and airways resistance (R) and dynamic lung compliance (Cdyn) measured continuously. Bronchoconstriction was produced by allowing the dogs to inhale 4 breaths of a histamine aerosol of 10 μm mean particle size through a tracheal cannula. The concentration of histamine solution from which the aerosol was generated was selected so that a change in R of 10–20 cm H_2O l^{-1} s^{-1} was produced. The concentrations used were 0.0625%–0.25%. The reflex component of the induced bronchoconstriction was determined by bilateral vagal cooling.

Histamine challenges were given every 30 min, and when 4 consistent reflex bronchoconstrictions had been produced the effects of 4 breaths of an aerosol of DSCG of 10 μm mean particle size, generated from either 1% or 2% solutions, on this bronchoconstriction were investigated. (The DSCG was given 10 min prior to the next histamine challenge.) The results of this study are shown in Figure 1.

After 1% DSCG there was some reduction in the

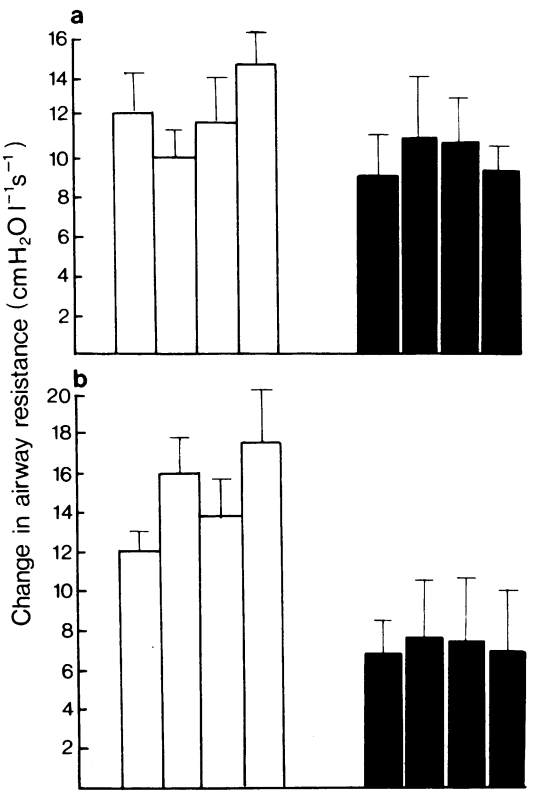

Figure 1 Changes in airway resistance produced by inhalation of 4 breaths of histamine aerosol of 10 μm mean particle size. The open histograms are control values and the closed histograms are the responses after inhalation of 4 breaths of an aerosol of DSCG of 10 μm mean particle size generated from a 1% solution (a) and a 2% solution (b). (Results are from 6 and 4 dogs respectively. Bars are s.e. mean.)