Uptake of debrisoquin and guanethidine by human blood platelets

SIR,—Although there has been much work on the uptake of 5-hydroxytryptamine (5-HT) by platelets, the possibility that these cells might also accumulate other substances has only recently been investigated. Solomon & Zieve (1967) have described the uptake of histamine, procaine, quinidine and reserpine by platelets, energy-dependent mechanisms being involved in the uptake of quinidine.

Since it is known that guanethidine is selectively taken up into sympathetic nerve endings (Schanker & Morrison, 1965; Chang, Costa & Brodie, 1965; Boullin, 1966, 1968), and recent work indicates that the uptake mechanism that concentrates 5-HT in platelets resembles the uptake mechanism of the sympathetic neuron (Pletscher, 1968), we have investigated the uptake of the anti-hypertensive drugs debrisoquin and guanethidine into human blood platelets suspended in normal plasma at 37°, using the technique described by Stacey (1961) for 5-HT. Tritiated guanethidine (Boullin, 1968) and carbon-14 labelled debrisoquin (specific activity 0·9 μc/mg) were used.

Both compounds were taken up by platelets suspended in plasma containing concentrations between 10^{-6} and 10^{-4}M. The ratio of the concentration of drug/ml of packed platelets (C_1) to the concentration/ml of plasma (C_0) varied between 6:1 and 25:1 at the end of 90 min incubation (Table 1). The accumulation process appeared to involve energy-dependent mechanisms, since the uptake of guanethidine and debrisoquin was reduced by 98% (s.e. $\pm$ 2%, 4 experiments with each compound) during incubation at 3° for 90 min. Efflux experiments with guanethidine showed that little drug was lost from platelets after uptake had occurred. In 4 experiments where platelets were re-suspended in drug-free plasma after an initial incubation for 90 min in medium containing 10^{-5}M guanethidine, 9·3% (s.e. $\pm$ 1·3%) was lost during the first 30 min re-incubation, but efflux then diminished.

Our finding that blood platelets can take up antihypertensive drugs until the concentration in the cells is 25 times greater than in the plasma, raises the possibility that this accumulation may be of some significance. Hardisty & Stacey (1955) reported that whole blood contains 4·2 μl platelets/ml, and our results agree with this. On this basis it may be calculated that, if the initial plasma level of drug is 1 μg/ml, 4 μl platelets will take up 0·1 μg if the C_1/C_0 ratio is 25:1. In other words the final distribution of drug in blood will be 90% in platelets and 10% in plasma. As guanethidine is neither lost from, nor metabolized by platelets (unpublished observations), the platelet-bound fraction will represent an increasing proportion of the total blood content as plasma levels decline due to metabolism. For example, if the plasma level declines by 90% over 40 hr, the platelet-bound portion will then represent 50% of the total. Clearly the actual proportion which the platelet-bound fraction represents will depend on the degree of uptake and the rate of decline

TABLE 1. UPTAKE OF DEBRISOQUIN AND GUANETHIDINE BY BLOOD PLATELETS

Drug	Concentration ratio C_1/C_0		
	Initial plasma concentration (M)		
	10^{-6}	10^{-5}	10^{-4}
Debrisoquin	—	14·5 ± 2·6	6·2 ± 0·3
Guanethidine	25·1 ± 1·6	20·1 ± 0·7	11·0 ± 1·0

C_1/C_0 is the ratio of the concentration of drug/ml packed platelets: concentration/ml plasma at the end of incubation.
Results are the mean ± s.e. obtained in 4–5 experiments.

of plasma levels, the above calculations being based on available data for debrisoquin plasma levels in man (Roche Products, Ltd., 1967).

Since the experiments described were carried out under conditions which may be considered to approximate to those occurring *in vivo* in man, there seems to be a *prima facie* case for considering that uptake of the above compounds may occur in patients undergoing anti-hypertensive therapy, and that any circumstance that interferes with the uptake of debrisoquin or guanethidine into platelets, or causes the discharge of these drugs from the platelets, may alter the magnitude and duration of their clinical effects.

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Absence of inhibitory effects of catecholamines on lower vertebrate arterial strip preparations

SIR,—Many pharmacological studies on spiral strips of large arteries from mammals have been reported and both α- and β-adrenotrophic receptors have been demonstrated (Furchgott, 1952, 1954; Furchgott & Bhadrakom, 1953; Bevan, 1960; Maxwell, 1965; Paterson, 1965). In the present work, the pharmacological responses of spiral strips of arteries from lower vertebrates have been examined as part of an investigation of the evolution of the autonomic innervation of the vasculature.

Spiral strips were cut from both right and left systemic arteries of the sleepy lizard (*Tiliqua rugosa*), the toad (*Bufo marinus*) and from the ventral aorta of the trout (*Salmo trutta*) and the eel (*Anguilla occidentalis australis*). The arterial strips from the sleepy lizard and toad were suspended in McKenzie solution as used by Campbell, Burnstock & Wood (1964). The teleost arterial strips were suspended in a modified Krebs solution as used by Bülbring (1953). Recordings were made at 25° either with an isotonic frontal writing lever or isometrically with a tension transducer.

In the lizard, toad, trout and eel, adrenaline tartrate and noradrenaline bitartrate monohydrate caused contraction of the arterial strips. The threshold concentration (salt) for contraction of the systemic artery of the sleepy lizard