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LIBERATION OF CATECHOLAMINES FROM BLOOD PLATELETS

ALFRED PLETSCHER

Department of Research, Kantonsspital Basel, Hebelstrasse 20,
CH-4031 Basel, Switzerland

1 Platelet-rich plasma (PRP) of guinea-pigs with or without reserpine was preincubated either with [^{14}C]-5-hydroxytryptamine ([^{14}C]-5-HT) plus [^{3}H]-dopamine or with [^{14}C]-5-HT plus [^{3}H]-noradrenaline ([^{3}H]-NA). After isolation on two successive dextran gradients the double-labelled platelets were incubated in Tris-buffer in the presence or absence of various drugs. The decrease in radioactivity in the platelets was measured in order to determine the amount of the amine that had been liberated.

2 Spontaneous liberation of the labelled amines was more marked in reserpine-treated platelets than in normal ones and somewhat more pronounced for the ^{3}H-catecholamines than for [^{14}C]-5-HT.

3 The reserpine-like benzoquinolizine, Ro 4-1284, caused liberation of all three labelled amines in normal but not in reserpine-treated platelets. More [^{3}H]-dopamine was liberated than [^{14}C]-5-HT and less [^{3}H]-NA.

4 The arylalkylamines, tyramine and *p*-chloromethamphetamine (PCMA), liberated all three labelled amines from normal platelets, and [^{14}C]-5-HT and [^{3}H]-dopamine, but not [^{3}H]-NA from reserpine-treated ones. In normal platelets dopamine was reduced to a greater extent than [^{14}C]-5-HT and [^{3}H]-NA to a smaller extent, whereas in reserpine-treated platelets [^{14}C]-5-HT was more markedly diminished than [^{3}H]-dopamine.

5 The 5-HT uptake inhibitor, imipramine, had little influence on the spontaneous and drug-induced liberation of [^{14}C]-5-HT and [^{3}H]-dopamine.

6 It is concluded that ^{3}H-catecholamines like [^{14}C]-5-HT are mostly localized in the granular pool of platelets; the three drugs tested liberate [^{3}H]-dopamine [^{3}H]-NA and [^{14}C]-5-HT from the granular pool. Ro 4-1284 does not liberate ^{3}H-catecholamines and [^{14}C]-5-HT from extragranular sites whereas tyramine and PCMA also act on the extragranular pool of [^{3}H]-dopamine and [^{14}C]-5-HT but not [^{3}H]-NA.

7 The liberation of catecholamines from platelets differs from that of 5-HT in several respects and platelets are only partly comparable to neurones as far as drug-induced liberation of biogenic amines is concerned.

Introduction

Blood platelets and 5-hydroxytryptamine (5-HT)-neurones have various similarities. For instance, both platelets and 5-HT-neurones possess specific, high affinity uptake mechanisms for 5-HT at the plasma membrane, with similar K_m values, and inhibitors of this uptake have similar orders of potency in both types of cells. Furthermore, those drugs (e.g. reserpine-like compounds and arylalkylamines) which cause liberation of 5-HT from neurones have the same effect in platelets (see Pletscher, 1978).

The uptake of dopamine and noradrenaline (NA) by platelets differs from that of 5-HT and is also different from the uptake of catecholamines by neurones. In fact, the K_m values for dopamine and NA in platelets are several orders higher than those for 5-HT in platelets and those for catecholamines in neurones (Pletscher, 1978; Pletscher, Laubscher, Graf & Sauer, 1979). However, it has been demonstrated that platelets contain catecholamines as well as 5-HT, although in a concentration several orders lower, probably due to the less efficient uptake mechanism at the plasma membrane (Da Prada & Picotti, 1979). Both endogenous and exogenous catecholamines show subcellular distributions resembling those of 5-HT (Da Prada & Pletscher, 1969; Da Prada & Picotti, 1979) indicating that a large part of the catecholamines is stored in subcellular organelles, probably the 5-HT-granules. In neurones, also, catecholamines are stored in subcellular granules or vesicles, in a similar way to 5-HT. Thus, drugs causing catecholamine liberation from neurones might also be expected to act similarly on platelets.

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The present work indicates that various drugs which liberate 5-HT also liberate dopamine and NA from platelets, not only from the granular, but also partly from the extragranular pools. However, the drug-induced liberation of catecholamines from platelets differs from that of 5-HT in several respects and also seems to be only partially comparable to that in neurones.

Methods

Labelling and isolation of platelets

Female guinea-pigs, Himalayan spotted, 600 to 800 g, were bled under light ether anaesthesia through a polyethylene cannula inserted in a carotid artery. The whole blood was collected in plastic tubes and mixed with 1/10 vol. 3.8% sodium citrate.$2H_2O$. Platelet-rich plasma (PRP) was prepared by centrifugation of the whole blood at 600 *g* for 10 min.

The platelets were then double-labelled by incubation of the PRP at 37°C for 80 min with 10^{-7} M [^{14}C]-5-HT plus 5×10^{-8} M [^{3}H]-dopamine or with 10^{-7} M [^{14}C]-5-HT plus 5×10^{-8} M [^{3}H]-NA. In some of the experiments the PRP was preincubated for 10 min with reserpine (added to the PRP as a 2×10^{-3} M solution in glacial acetic acid to give a final concentration of 2×10^{-6} M) before addition of the radioactive amines and incubation for a further 80 min. The PRP (20 ml) was then put on a gradient consisting of 4 ml 20% dextran T_{10} (bottom layer) and 7 ml 10% dextran (upper layer), containing 1% (w/v) bovine albumin, 0.15% glucose and 0.3% Na-citrate.$2H_2O$. After centrifugation for 10 min at 4500 *g* the platelets which banded between the two layers were removed and diluted with 7 to 8 volumes Tris-buffer (per litre: NaCl 8.21 g, KCl 9.57 g, glucose 1.01 g, Tris (hydroxymethyl)-aminomethane 0.93 g, trisodium citrate.$2H_2O$ 3.80 g) (Graf, Laubscher, Richards & Pletscher, 1979). This suspension was put on the dextran gradient for a second time and centrifuged as before. These operations were all carried out at 4°C. The platelets were then diluted with about 1 volume Tris-buffer, counted in a Coulter counter and further diluted with Tris-buffer to give a final platelet concentration of 3 to 5×10^{8}/ml.

Amine liberation

Aliquots of 0.1 ml of the final platelet suspension were added to 1.9 ml Tris-buffer alone or containing the drugs as required for the experiment. The Tris-buffer had been kept at 37°C for 15 min before addition of the platelets. After incubation with gentle shaking at 37°C for various periods the platelets were cooled in ice water and centrifuged at 2500 *g* and 4°C. The supernatant was decanted, the tube walls were cleaned with a cotton stick and the platelet pellet was dissolved in 0.1 ml buffer plus 0.1 ml Triton 1%. The radioactivity was then measured in a liquid scintillation counter with windows for ^{14}C and ^{3}H. Platelets which had been washed before dissolving in Triton gave virtually the same results as those in which the washing procedure had been omitted.

Electron micrographs of platelets incubated with and without the drugs (arylalkylamines 10^{-3} M, Ro 4-1284 10^{-6} M) did not reveal relevant platelet damage.

Mathematical calculations

The amount of the labelled amines remaining in the platelets after incubation is given as a percentage of that present before incubation (time course experiments) or of that found in platelets incubated in a drug-free medium (drug experiments). The [^{14}C]-5-HT values from the experiments with [^{14}C]-5-HT plus [^{3}H]-dopamine and from those with [^{14}C]-5-HT plus [^{3}H]-NA were averaged together, since the results for [^{14}C]-5-HT were practically the same in both types of experiment. The absolute values of the labelled amines were calculated according to the number of platelets present. Statistical analysis of the results was performed using Student's *t* test.

Materials

All the substances used were of analytical grade, most of them being obtained from commercial sources. Ro 4-1284 (2-hydroxy-2-ethyl-3-isobutyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11-bH-benzo-{a} quinolizine) and *p*-chlormethamphetamine (PCMA; 3-chloro-N, α-dimethylphenylethylamine) were generous gifts from F. Hoffmann-La Roche Inc., Basel. The 5-hydroxy [side chain-2-^{14}C]tryptamine creatinine sulphate ([^{14}C]-5-HT; sp. act. 58 mCi/mmol), the 3,4-dihydroxy [ring-G-^{3}H] phenylethylamine hydrochloride (sp. act. 6.2 Ci/mmol) and the 1-[7,8-^{3}H]-noradrenaline ([^{3}H]-NA; sp. act. 28.3 Ci/mmol) were purchased from the Radiochemical Centre, Amersham.

Results

Absolute values

Before incubation in the artificial medium (time 0 in Figure 1) normal platelets had an absolute content of [^{14}C]-5-HT, [^{3}H]-dopamine and [^{3}H]-NA (in pmol/10^{8} platelets) of 31.5 ± 1.5, 0.92 ± 0.10 and 0.10 ± 0.01 respectively whereas the content of these labelled amines in reserpine-treated platelets was 8.5 ± 1.8, 0.05 ± 0.01 and 0.02 ± 0.00 respectively.

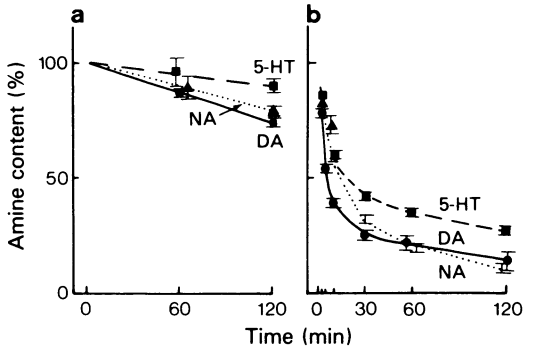

Figure 1 Spontaneous decrease of [^{14}C]-5-hydroxytryptamine (5-HT, ■), [^{3}H]-dopamine (DA, ●) and [^{3}H]-noradrenaline (NA, ▲) in normal (a) and reserpine-treated (b) platelets. The points are averages with s.e. mean of 3 (dopamine and NA) and 6 (5-HT) experiments and indicate the amine content of platelets as a percentage of that before incubation. Significance: Normal platelets: 5-HT 120 min: $P < 0.01$ versus dopamine and NA; reserpine-treated platelets: dopamine 5 and 10 min: $P < 0.01$ versus 5-HT and NA; 5-HT 30 to 120 min: $P < 0.01$ versus dopamine and NA.

Spontaneous liberation

In normal platelets all three labelled amines decreased linearly during incubation for 2 h. The decrease of [^{3}H]-dopamine and [^{3}H]-NA was more marked (26 and 21% after 2 h) than that of [^{14}C]-5-HT (10%). In reserpine-treated platelets all three labelled amines decreased more markedly than in normal platelets, the decrease following a virtually exponential course. Again, the diminution of [^{3}H]-DA and [^{3}H]-NA (86 and 81%) was more pronounced than that of [^{14}C]-5-HT (73%) (Figure 1).

Benzoquinolizine Ro 4-1284

In normal platelets, 10^{-6} M Ro 4-1284 caused decreases of [^{14}C]-5-HT, [^{3}H]-dopamine and [^{3}H]-NA which, as previously shown for 5-HT (Picotti, Da Prada & Pletscher, 1976), followed virtually exponential courses for 1 to 2 h. Increasing concentrations of the drug induced a progressive decline in the contents of the three amines. However, Ro 4-1284 decreased [^{3}H]-dopamine to a greater extent than [^{14}C]-5-HT and [^{3}H]-NA less (Figure 2).

Ro 4-1284 did not cause any change in the contents of [^{14}C]-5-HT, [^{3}H]-dopamine or [^{3}H]-NA in reserpine-treated platelets during the 2 h of the experiment (Figure 2).

Arylalkylamines

In normal platelets tyramine and PCMA (10^{-3} M) caused decreases of [^{14}C]-5-HT, [^{3}H]-dopamine and [^{3}H]-NA which were virtually exponential for 2 h (as shown previously with PCMA for 5-HT; Bartholini &

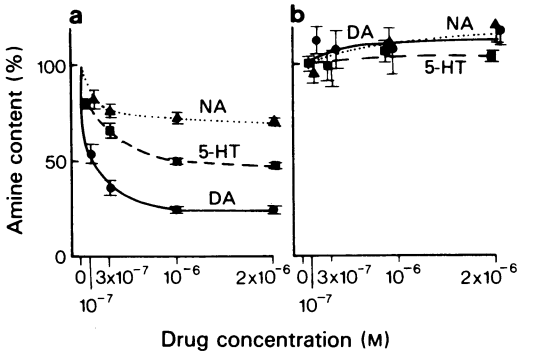

Figure 2 Effect of incubation for 2 h with various concentrations of Ro 4-1284 on the content of [^{14}C]-5-hydroxytryptamine (5-HT, ■), [^{3}H]-dopamine (DA, ●) and [^{3}H]-noradrenaline (NA, ▲) in normal (a) and reserpine-treated (b) platelets. The points are averages with s.e. mean of 3 to 4 (dopamine and NA) and 6 to 8 (5-HT) experiments and indicate the amine content of platelets as a percentage of that present in platelets incubated for 2 h in drug-free medium. Significance: Normal: dopamine 10^{-7} to 2×10^{-6}: $P < 0.01$ versus 5-HT and NA; NA 3×10^{-7} to 2×10^{-6}: $P < 0.01$ versus 5-HT.

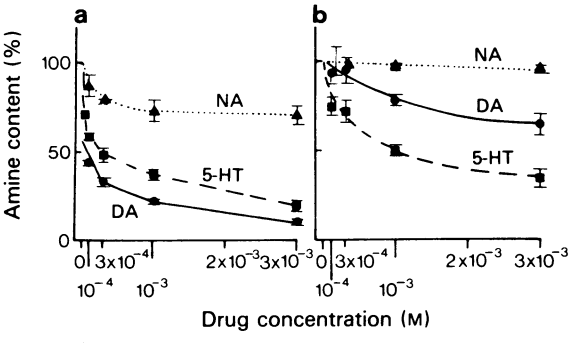

Figure 3 Effect of incubation for 1 h with various concentrations of tyramine on the contents of [^{14}C]-5-hydroxytryptamine (5-HT, ■), [^{3}H]-dopamine (DA, ●) and [^{3}H]-noradrenaline (NA, ▲) in normal (a) and reserpine-treated (b) platelets. The points are averages with s.e. mean of 3 to 4 (dopamine and NA) and 6 to 8 (5-HT) experiments and indicate the amine content of platelets as a percentage of that present in platelets incubated for 1 h in drug-free medium. Significance: Normal: 5-HT 10^{-4} to 3×10^{-3}: $P < 0.01$ versus dopamine and NA, dopamine 10^{-4} to 3×10^{-3}: $P < 0.01$ versus NA; reserpine-treated 5-HT 10^{-4} to 3×10^{-4}: $P < 0.01$ versus dopamine and NA, NA 10^{-3} and 3×10^{-3}: $P < 0.01$ versus dopamine.

Pletscher 1964). With increasing concentrations of the drugs the decrease of the labelled amines became progressively more pronounced. Both tyramine and PCMA diminished [^{3}H]-dopamine more than [^{14}C]-5-HT and [^{3}H]-NA less (Figure 3, Table 1). In reserpine-treated platelets the action of tyramine and PCMA on the labelled amines differed from that in normal platelets. Both drugs diminished [^{3}H]-dopamine and [^{14}C]-5-HT, but in concentrations up to 2 and 3×10^{-3} M they no longer caused a decrease in the [^{3}H]-NA content; furthermore, [^{14}C]-5-HT was affected to a greater extent than [^{3}H]-dopamine (Figure 3).

Imipramine

In platelets incubated with imipramine (10^{-7} M), which completely blocks the uptake of 5-HT (Laubscher & Pletscher, 1979a), the spontaneous decrease of [^{14}C]-5-HT remained less than that of [^{3}H]-dopamine. Also, Ro 4-1284, tyramine and PCMA still caused a smaller diminution of [^{14}C]-5-HT than of [^{3}H] dopamine in the presence of imipramine (Table 1).

Discussion

The spontaneous liberation (leakage) of labelled catecholamines from normal platelets was greater than that of [^{14}C]-5-HT, which is in agreement with previous findings in human platelets (Barbeau, Campanella, Butterworth & Yamada, 1975; Boullin & O'Brien, 1970; Mattiasson, Mattiasson & Hood, 1979). The liberation of all three amines was strongly enhanced in reserpine-treated platelets in which granular storage is abolished. This indicates that in normal platelets the catecholamines, like 5-HT, are mainly accumulated and retained in storage granules, a conclusion in agreement with previous observations on the subcellular distribution of labelled dopamine, NA and 5-HT in platelets (Da Prada & Pletscher, 1969). It is also supported by preliminary experiments in which thrombin (which predominantly liberates the granular constituents of platelets, e.g. 5-HT: Reimers, Kinlough-Rathbone, Cazenave, Senyi, Hirsch, Packham & Mustard, 1976) caused marked, virtually identical decreases in [^{3}H]-dopamine, [^{3}H]-NA and [^{14}C]-5-HT. A similar conclusion has been reached earlier with regard to the storage of [^{3}H]-adrenaline (Born & Smith, 1970). The finding that spontaneous liberation of labelled catecholamines was more pronounced than that of [^{14}C]-5-HT cannot be explained by a reuptake of [^{14}C]-5-HT, although the latter has a more efficient transport mechanism at the plasma membrane. In fact, even in the presence of imipramine (10^{-7} M), the decrease of [^{3}H]-dopamine was greater than that of [^{14}C]-5-HT.

The benzoquinolizine, Ro 4-1284 (Pletscher, Brossi & Gey, 1962) was ineffective in reserpine-treated platelets, although it decreased the contents of the amines in normal platelets. In these, a greater proportion of the (reduced) intracellular amines are probably stored at extragranular sites than in normal platelets. This shows that Ro 4-1284 acts exclusively on the

Table 1 Spontaneous and drug-induced decrease of [^{14}C]-5-hydroxytryptamine (5-HT) and [^{3}H]-dopamine (DA) in platelets of guinea-pigs incubated with or without imipramine 10^{-7} M

	Platelet content of labelled amines			
	[^{14}C]-5-HT (%)		*[^{3}H]-DA (%)*	
Liberating agent	*Controls*	*Imipramine*	*Controls*	*Imipramine*
Spontaneous normal platelets	92.0 ± 3.4	90.1 ± 2.2	77.8 ± 5.0*	76.8 ± 4.6†
Spontaneous reserpine-treated	27.7 ± 4.3	20.7 ± 0.6	16.1 ± 3.6*	14.7 ± 2.1†
Ro 4-1284	46.1 ± 1.2	45.0 ± 2.1	28.3 ± 0.6**	29.4 ± 1.4†
Tyramine	50.6 ± 2.1	55.4 ± 1.9	37.0 ± 0.6**	36.4 ± 1.4†
PCMA	62.2 ± 4.3	62.7 ± 3.1	37.1 ± 2.6**	37.2 ± 2.4†

For the spontaneous decrease and the decrease induced by 10^{-6} M Ro 4-1284, platelets were incubated for 2 h, for the decrease induced by 3×10^{-4} M tyramine and 3×10^{-4} M *p*-chlormethamphetamine (PCMA) the incubation was carried out for 1 h. The figures are averages with s.e. mean of 3 experiments and each indicate the amine content of platelets as a percentage of that before incubation (spontaneous decrease) or of that present after incubation without drugs (drug experiments).
Absolute amounts of labelled amines at zero time: see results.
Significance: * $0.01 < P < 0.05$, ** $P < 0.01$ versus [^{14}C]-5-HT of controls
† $P < 0.01$ versus [^{14}C]-5-HT of imipramine experiments

granular amines, confirming and extending previous findings from 5-HT uptake experiments (Laubscher & Pletscher, 1979a, b).

The arylalkylamines, tyramine and PCMA, also acted on granular [^{3}H]-dopamine and [^{14}C]-5-HT. Thus, the drugs caused a marked decrease (over 80%) of [^{3}H]-dopamine and [^{14}C]-5-HT in normal platelets, where the amines are preferentially stored in the granular pool. The less marked decrease of [^{3}H]-NA was probably also due to liberation from the granular pool since the arylalkylamines (and in preliminary experiments also octopamine, a metabolite of tyramine) did not liberate extragranular [^{3}H]-NA (no effect in reserpine-treated platelets). However, tyramine and PCMA, in contrast to Ro 4-1284 caused liberation of extragranular [^{3}H]-dopamine and [^{14}C]-5-HT as indicated by their action in reserpine-treated platelets.

The finding that all the drugs decreased [^{14}C]-5-HT to a smaller extent than [^{3}H]-dopamine in normal platelets cannot be explained by a reuptake of liberated [^{14}C]-5-HT, as seen from the experiments with imipramine.

Based on the evidence available at the moment, platelets of guinea-pigs seem to be comparable to a limited extent to monoaminergic neurones regarding amine liberation. The pattern of action of Ro-1284 was similar in platelets and in neurones, but the decrease in NA was more marked in the latter (Pletscher, Da Prada, Burkard & Tranzer, 1968). Arylalkylamines were about equally potent in liberating amines from neurones *in vitro* (Ng, Chase & Kopin, 1970; Colburn & Kopin, 1972; Kant & Meyerhoff, 1978; Hefti & Lichtensteiger, 1978; Bagchi & Smith, 1979) and from platelets. Furthermore, PCMA liberated 5-HT and dopamine but not NA from extragranular sites in both cell types *in vitro* (Ross, 1977; Ross, 1979), however, in the brain *in vivo*, the drug caused a virtually selective decrease of 5-HT (Pletscher, Bartholini, Bruderer, Burkard & Gey, 1964). Finally, in neuronal tissue, tyramine did not affect either extragranular 5-HT or NA (Fischer & Kopin, 1964; Ross, 1979) whereas in platelets the drug decreased extragranular 5-HT.

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