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SHAPE CHANGE OF BLOOD PLATELETS—A MODEL FOR CEREBRAL 5-HYDROXYTRYPTAMINE RECEPTORS?

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1 In blood platelets of rabbits isolated by a stractan gradient and incubated in a protein-poor medium, tryptamine, 5-hydroxytryptamine (5-HT) and derivatives, quipazine and mescaline caused a shape change. This shape change was inhibited by low concentrations of methysergide.

2 The most potent antagonists of the 5-HT-induced shape change included ergoline derivatives and neuroleptic drugs, which showed high stereoselectivity.

3 (+)-Lysergic acid diethylamide ((+)-LSD), psilocine and some N′,N′-dimethylated tryptamines acted as mixed agonist-antagonists.

4 The compounds found to be agonists or mixed agonist-antagonists on platelets have previously been shown to act also as 5-HT agonists in the central nervous system (CNS).

5 With regard to 5-HT antagonists, the 5-HT receptors of platelets reacted differently from those described earlier in brain areas with dense 5-hydroxytryptaminergic innervation, but showed similarities to 5-HT receptors investigated previously in spinal cord, cerebral cortex and possibly reticular formation.

6 It is concluded that platelets may be considered with caution as models for some, but not for all, 5-HT receptors in the CNS.

Introduction

The dynamics of 5-hydroxytryptamine (5-HT) in platelets, especially of its uptake, release and metabolism, show analogies with those of cerebral 5-HT neurones. However, in other aspects, e.g. synthesis and turnover of 5-HT, marked differences exist between these two cell types. Platelets have been considered, therefore, as furnishing limited models for the 5-HT neurones of the brain (Sneddon, 1973; Gordon & Olverman, 1978; Pletscher, 1978).

Blood platelets are also claimed to contain 5-HT receptors on their plasma membrane which seem to differ from receptors responding to other agents such as adenosine 5′-diphosphate (ADP), thrombin and collagen (Gordon, 1976; Kinlough-Rathbone, Packham, Reimers, Cazenave & Mustard, 1977). In fact, platelets react to 5-HT by a reversible shape change which induces increased light absorption and scattering and which may be followed by platelet aggregation (Born, 1970; Drummond, 1976). In addition, labelled 5-HT shows a reversible high affinity binding to the platelet membrane, and there is good correlation between the concentrations of various drugs which inhibit shape change and those interfering with binding (Drummond, 1976). The nature of the hypothetical 5-HT receptor of platelets has been studied by several authors using a variety of drugs and other compounds (Born, Juengjaroen & Michal, 1972; Drummond, 1976; Boullin & Glenton, 1978) from which studies it was concluded that the platelet receptor had the general characteristics of peripheral D-type receptors (Michal, 1969).

The possibility that 5-HT receptors of blood platelets might serve as models for those in the central nervous system (CNS) has not been systematically investigated. The present work deals with the pharmacological characteristics of the platelet shape change, which are compared with those of the 5-HT receptors in the brain, as described in the literature. The 5-HT-induced shape change was assumed to be a more direct functional correlate of receptor activity than platelet aggregation. It was measured in a protein-poor artificial medium, i.e. under conditions in which no aggregation occurs. Previous work has mainly been carried out with platelet suspensions relatively rich in protein, e.g. platelet-rich plasma in which the potency of action of some drugs, e.g. chlorpromazine, methysergide, mianserin, has been shown to be decreased by protein binding (Graf, Laubscher, Richards & Pletscher, unpublished observations).

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Methods

Materials

All the substances used were of analytical grade, most of them being obtained from commercial sources. (+)- and (−)-Lysergic acid diethylamide (LSD), psilocine and psilocybin were kindly donated by Sandoz Ltd, Basel, the sugar derivatives of 5-HT (Mester & Mester, 1976) by Professor L. Mester, Centre National de la Recherche Scientifique, Paris. The following drugs were synthesized by chemists of F. Hoffmann-La Roche & Co. Ltd, Basel: Ro 4-1284 (2-hydroxy-4-ethyl-3-isobutyl-9, 10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[a]quinolizine HCl) (Dr H. Bruderer), methiothepin (Dr E. Kyburz), (5R,8S)- and (5R,8R)-lisurid (Dr M. Gerecke), 5,6-dihydroxytryptamine (Dr A. Kaiser). Stractan II (a polyarabinogalactan mol. wt. ~ 30,000) was purchased as a crude powder from St. Regis, Lumber & Plywood Division, Libby, Montana, USA.

Preparation of stractan gradients

The purification of the crude stractan powder was carried out according to Corash, Piomelli, Chen, Seaman & Gross (1974) and Corash, Tan & Gralnick (1977) with the following modifications: after the crude powder had been dissolved in distilled water (50% w/w) at 4°C overnight, the solution, in volumes of about 300 ml, was dialysed for 5 h at 4°C against 4000 ml 2× distilled water using a Union Carbide dialysis membrane. The non-dialysable part was then passed twice through columns of amberlite MB-3 as described previously. The osmolarity of the stractan solution was measured with a Knaur freezing point depression osmometer. The solution (of less than 100 mosm/l) was supplemented with 1/20 vol of 0.3 M phosphate buffer pH 7.4, then treated as described and kept at −20°C. For the preparation of two gradients one aliquot was thawed, of which 7 ml was diluted to 20% and 5 ml to 10% (v/v) with BSG citrate: (g/l) NaCl 6.832, trisodium citrate x $2H_2O$ 4.0, glucose 2.0, Na_2HPO_4 1.22, KH_2PO_4 0.218, pH 7.4, 290 mosmolar. Seven ml of the 10% solution was then gently layered on to 5 ml of the 20% solution in 3.5 × 1 inch cellulose nitrate tubes (Beckman).

Isolation of platelets

New Zealand white rabbits (about 3 kg, either sex) were bled under light ether anaesthesia through a polyethylene cannula inserted in a carotid artery. The whole blood was collected in a plastic vial and mixed with 12/100 vol acid citrate-dextrose (ACD): 0.8% citric acid, 2.5% trisodium citrate-dihydrate, 2.5% dextrose (all w/v), pH 6.5. Platelet-rich plasma (PRP) was prepared by centrifugation of the whole blood at 400 *g* for 10 min in plastic tubes. After dilution of the PRP with BSG citrate 3:1 (v/v), 20 ml of this suspension was put on the stractan gradient and centrifuged for 10 min at 2200 *g* in a Heraeus UJ-2 centrifuge. The tube was punctured at the bottom with a hollow needle, and the platelets which had banded between the 20% and 10% layer of the stractan gradient were transferred to a plastic tube. The recovery of the platelets was 60 to 70% compared to the PRP.

The platelet concentrate was diluted to about 5 times its volume with BSG citrate, the number of platelets was counted in a Coulter counter and the platelet concentration adjusted to 1.5×10^8 per ml with BSG citrate; the dilution factor was about 30 compared with the original platelet concentrate. Samples of 1 ml of the final platelet suspension with a protein content of about 0.03% were preincubated at 37°C for 35 min before addition of the compounds to be tested; all other operations were carried out at room temperature. Transmission and scanning electron-microscopy showed no morphological differences between platelets isolated with the stractan gradient and those in PRP (unpublished observations).

Measurement of shape change

The shape change in platelet suspensions was determined with a Born Mark 3 aggregometer by measuring the maximal light absorption at 37°C (M in Figure 1) (Michal & Born, 1971; Segal, 1976). The samples were stirred with a Teflon-covered magnetic stirrer at about 900 revolutions per min. The results were recorded on a Rikadenki recorder B-361 with a full scale deflection of 50 mV. The reversible shape change of the platelets due to the starting and stopping of the stirrer (Latimer, Born & Michal, 1977) was used to adjust the sensitivity of the aggregometer. Agonists and antagonists were added in a volume of 5 to 15 µl, the antagonist being added 1 min before the agonist. The compounds were dissolved in H_2O, diluted citric or acetic acid or methanol. Platelet suspensions supplemented with the solvents alone were used as controls. The shape change induced by 5-HT in platelets suspended in BSG citrate was virtually identical to that occurring in PRP (Graf, Laubscher, Richards & Pletscher, unpublished observations).

Calculations

The calculations were based on the maximal shape change which occurred about 1 min after addition of an agonist to the platelet suspension (M in Figure 1). EC_{50} denotes the molar concentration of an agonist inducing half maximal shape change, and the IC_{50} indicates the molar concentration of an antagonist inducing a 50% inhibition of the maximal shape

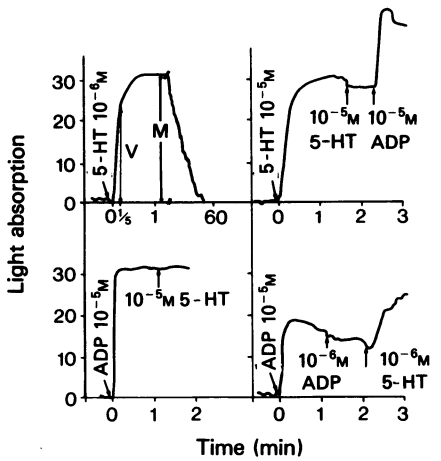

Figure 1 Platelet shape change induced by 5-hydroxytryptamine (5-HT) and adenosine 5'-diphosphate (ADP) in rabbit platelets. M = maximal shape change, V = shape change occurring within 12 s. Results of typical experiments. The ordinate scale indicates the light absorption expressed as deflection on the recorder scale in mV.

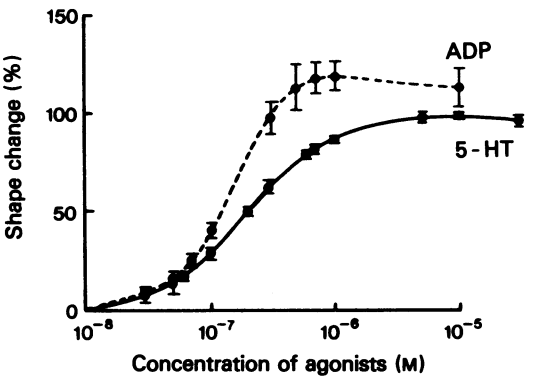

Figure 2 Platelet shape change induced by various concentrations of 5-hydroxytryptamine (5-HT) and adenosine 5'-diphosphate (ADP) measured after 1 min. The maximal shape change induced by 10^{-5} M 5-HT was taken as 100%. Each point indicates mean of 4 experiments with different rabbits; vertical lines show s.e. mean. Computer fitted curves.

change caused by an agonist. EC_{50}, IC_{50} as well as the 95% confidence limits were calculated on an IBM/350 computer using an iterative non-linear least squares regression to a log-logistic function. When the calculation was based on the shape change occurring 12 s after addition of an agonist to the platelet suspension (V in Figure 1 = 100%), the values for the EC_{50} and IC_{50} were similar or not markedly (at the most by a factor of 2–3) different from those calculated on the basis of the maximal shape change. Therefore, the shape change after 12 s (which might also depend on the speed of the shape change reaction) was not considered in the present work.

Results

5-Hydroxytryptamine and adenosine diphosphate

Both 5-HT (10^{-6} M) and ADP (10^{-6} M) caused a reversible increase of light absorption in platelet suspensions indicating a shape change of the platelets. It attained a maximum within about 1 min; the maximum persisted for several minutes and then decreased towards control values within 1 h. The light absorption increased with rising concentrations of 5-HT and ADP reaching maximal values at 10^{-5} 5-HT and 7×10^{-7} M ADP. ADP caused a greater maximal effect than 5-HT. The concentrations inducing half maximal light absorption (EC_{50}) were slightly but significantly different, i.e. 2.1×10^{-7} M for 5-HT and 1.3×10^{-7} M for ADP ($P < 0.05$) (Figures 1 and 2, Table 1). After maximal stimulation of the platelets with 5-HT (10^{-5} M), addition of ADP (10^{-5} M) caused a further increase in light absorption. In contrast, platelets maximally stimulated by ADP (10^{-5} M) did not react further to 5-HT (10^{-5} M). However, in those platelets in which the reaction to ADP was lower than normal (which occurred in rare instances) 5-HT caused an additional increase in shape change (Figure 1).

Agonists

Among a great variety of compounds (Tables 1 to 3), including biogenic amines, psychotropic and other drugs, only those indicated in Table 1 induced platelet shape change. The shape change caused by these agonists (except ADP) showed a similar time course to that due to 5-HT and was inhibited by small concentrations (10^{-8} to 10^{-9} M) of methysergide (Table 4). The 5-HT agonists differed to some extent from each other as regards EC_{50} as well as maximal effect. Besides ADP, only compounds closely related to 5-HT, such as sugar derivatives of 5-HT and 5,6-dihydroxytryptamine, showed an approximately equal maximal effect when compared with 5-HT, whereas the maximal effects of the other compounds, especially of (+)-LSD, psilocine and N',N'-dimethylated tryptamines, were lower than that of 5-HT (Table 1). N',N'-dimethyltryptamine had an inconsistent effect exhibiting no detectable agonist action in 2 of the 7 experiments. (−)-LSD and psilocybin in concentrations up to 10^{-4} M did not induce platelet shape change.

Table 1 Putative 5-hydroxytryptamine (5-HT) receptor agonists inducing platelet shape change

Compound	n	EC_{50} (M)	*95% confidence limits*	*Maximal shape change (%) ± s.e.mean*
(+)-LSD	8	2.8×10^{-8}	1.0–6.5	16.9 ± 1.7
Psilocine	3	8.0×10^{-8}	2.8–25.2	8.6 ± 1.3
Adenosine 5'-diphosphate	5	1.3×10^{-7}	1.0–1.7	119.9 ± 4.5
N',N'-dimethyl-5-HT	3	1.3×10^{-7}	0.8–2.1	27.0 ± 2.1
5-Hydroxytryptamine	4	2.1×10^{-7}	1.9–2.2	100
N',N'-dimethyl-5-methoxy-tryptamine	5	2.1×10^{-7}	0.4–9.6	23.0 ± 3.6
N',N'-dimethyltryptamine	7	7.2×10^{-7}	1.9–28.1	7.1 ± 2.0
Tryptamine	5	9.9×10^{-7}	7.9–12.3	63.5 ± 4.1
Quipazine	3	2.0×10^{-6}	1.4–2.6	43.4 ± 2.5
5,6-Dihydroxytryptamine	3	3.0×10^{-6}	2.5–3.7	93.9 ± 2.4
N-desoxyribose-5-HT	4	5.8×10^{-6}	4.1–7.9	93.0 ± 7.6
N-desoxyfructose-5-HT	4	1.7×10^{-5}	1.5–2.2	92.6 ± 14.0
5,7-Dihydroxytryptamine	3	2.0×10^{-5}	1.4–2.7	46.1 ± 5.5
Mescaline	4	2.2×10^{-5}	1.6–3.1	46.2 ± 3.4

EC_{50} indicates concentration of an agonist inducing half maximal shape change. The maximal shape change induced by 5-HT was taken as 100%. n = number of experiments with platelets from different rabbits.

Table 2 Compounds having no effect or inducing unspecific platelet shape change

No effect	*Unspecific shape change*	*Threshold conc (M)*
Histamine	Methiothepin	2×10^{-6}
Dopamine	Methergoline	3×10^{-6}
Noradrenaline	Chlorpromazine	3×10^{-6}
Adrenaline	Haloperidol	3×10^{-6}
Tyramine	Reserpine	3×10^{-6}
5-Hydroxytryptophan	Cyproheptadine	10^{-5}
5-Hydroxytryptophol	Chlorimipramine	10^{-5}
5-Hydroxyindoleacetic acid	Desmethylimipramine	10^{-5}
(−)-LSD	(+)-Butaclamol	10^{-5}
Psilocybin	(−)-Butaclamol	10^{-5}
Morphine	Phenoxybenzamine	10^{-5}
Tetrodotoxin	Mianserin	2×10^{-5}
Dexamphetamine	(±)-Propanolol	7×10^{-5}
Hexobarbitone	Phentolamine	10^{-4}
Tolazoline	Ro 4-1284	10^{-4}
Aspirin		
Indomethacin		
Theophylline		
Aminophylline		

'No effect' means no specific shape change or relevant inhibition of the 5-hydroxytryptamine (5-HT, 10^{-6} M)-induced shape change by drug concentrations up to 10^{-4} M. 'Threshold concentration' is the drug concentration at which the unspecific shape change starts to develop. Each drug was tested on three platelet suspensions obtained from different rabbits.

Antagonists

The most potent antagonists of the 5-HT-induced shape change were ergoline derivatives, cyproheptadine, mianserin, cinanserin, and neuroleptics like spiroperidol, methiothepin, chlorpromazine and (+)-butaclamol (IC_{50} 10^{-8} to 10^{-9} M). This group was followed by phenoxybenzamine, haloperidol, desmethylimipramine and chlorimipramine (IC_{50} 10^{-7} to 10^{-6} M). The other compounds tested showed an IC_{50} in the order of 10^{-6} M (apomorphine) or above. Psilocybin (up to 10^{-4} M) had no antagonistic effect. (−)-Butaclamol and (−)-LSD were less potent by at least 3 orders of magnitude than the respective (+)-isomers in inhibiting the 5-HT-induced shape change, whereas (5R,8R)-lisurid showed only a slightly, though significantly lower potency (about twice; $P < 0.05$) than the (5R,8S)-isomer (Tables 2 and 3). Some of the 5-HT agonists ((+)-LSD, psilocine, N′,N′-dimethylated tryptamines) which caused a considerably smaller maximal shape change than 5-HT, completely inhibited the 5-HT-induced shape change. Their IC_{50} was of the order of the EC_{50} of these compounds (Tables 1 and 3).

Methysergide and the neuroleptics, chlorpromazine and (+)-butaclamol, in concentrations up to 10^{-5} M (threshold for the unspecific shape change produced by the neuroleptics) did not antagonize the ADP-induced shape change.

Table 3 Antagonists of the 5-hydroxytryptamine (5-HT)-induced shape change

Compound	n	IC_{50} (M)	*95% confidence limits*
Spiroperidol	4	1.0×10^{-9}	0.9–1.2
Methiothepin	4	1.15×10^{-9}	1.1–1.2
Methergoline	4	1.3×10^{-9}	1.1–1.5
Cyproheptadine	3	2.1×10^{-9}	1.9–2.2
Mianserin	4	3.9×10^{-9}	3.0–5.0
Methysergide	3	6.2×10^{-9}	5.2–7.5
Chlorpromazine	3	6.8×10^{-9}	6.0–7.6
BOL-148	3	7.7×10^{-9}	6.4–9.4
(5R,8S)-Lisurid	4	8.2×10^{-9}	6.8–9.9
(+)-LSD	3	1.0×10^{-8}	0.9–1.1
(+)-Butaclamol	4	1.3×10^{-8}	1.1–1.6
(5R,8R)-Lisurid	4	1.4×10^{-8}	1.2–1.7
Cinanserin	4	2.0×10^{-8}	1.9–2.2
Phenoxybenzamine	4	9.2×10^{-8}	7.9–10.5
Haloperidol	3	1.8×10^{-7}	1.3–2.6
Psilocine	3	2.8×10^{-7}	2.4–3.3
Desmethylimipramine	4	4.1×10^{-7}	3.1–5.5
N′,N′-dimethyl-5-methoxytryptamine	5	4.1×10^{-7}	3.9–4.3
N′,N′-dimethyl-5HT	4	4.5×10^{-7}	3.9–5.3
Chlorimipramine	3	5.0×10^{-7}	3.3–7.4
N′,N′-dimethyl-tryptamine	4	1.2×10^{-6}	1.0–1.5
Apomorphine	4	1.3×10^{-6}	1.2–1.4
Phentolamine	3	2.3×10^{-6}	2.0–2.7
Yohimbine	4	1.0×10^{-5}	0.9–1.1
(±)-Propanolol	3	1.1×10^{-5}	0.8–1.6
Papaverine	3	1.3×10^{-5}	1.0–1.6
Fenfluramine	4	2.7×10^{-5}	2.1–3.4
Atropine	3	3.4×10^{-5}	2.6–4.5
(−)-LSD	3	7.9×10^{-5}	7.3–8.6
(−)-Butaclamol	3	$> 10^{-5}$	

The antagonists were added to the platelet suspension 1 min before 5-HT 10^{-6} M. IC_{50} indicates the molar concentration of an inhibitor inducing 50% inhibition of the maximal shape change due to 5-HT 10^{-6} M. n = number of experiments each with platelets from a different rabbit. BOL-148 = (+)-2-bromolysergic acid diethylamide.

Unspecific shape change

Relatively high concentrations of various drugs (Table 2) caused a shape change characterized by a continuous increase in light absorption for 5 to 20 min which was not antagonized by methysergide in concentrations up to 10^{-4} M. Since this shape change showed different characteristics from that described under 'Antagonists', it will not be dealt with in the following discussion.

Discussion

The present results with platelets in a protein-poor medium confirm and extend previous findings with PRP (Baumgartner & Born, 1969; Born *et al.*, 1972; Drummond, 1976; Michal & Motamed, 1976; Boullin & Green, 1976; Boullin & Glenton, 1978). The tryptaminergic receptor of the platelet membrane is clearly different from the ADP receptor, since ADP enhanced the maximal shape change obtained with 5-HT, and under certain conditions 5-HT enhanced the maximal shape change induced by ADP. Furthermore, the shape change due to 5-HT, but not that due to ADP, was inhibited by very small concentrations of ergoline derivatives and neuroleptic drugs. The tryptamine receptor showed a relatively high degree of specificity, since out of a variety of compounds only a few, i.e. those known to be tryptamine receptor agonists in other tissues, induced a shape change which was inhibited by methysergide. In addition, the receptor exhibited marked stereoselectivity for (+)-LSD and (+)-butaclamol and, as described earlier, for *cis*-chlorprothixene (Drummond, Whigham & Prentice, 1976).

Several of the compounds in Table 1 ((+)-LSD, psilocine, N',N'-dimethylated tryptamines) may be considered as mixed agonists-antagonists. These substances caused a much smaller maximal shape change than 5-HT, but completely inhibited the 5-HT-induced shape change.

Those substances which are generally thought to be 5-HT agonists in the CNS, e.g. tryptamine- and 5-HT-derivatives, (+)-LSD, quipazine, mescaline (Jacoby, Howd, Levin & Wurtman, 1976; Haigler & Aghajanian, 1977; de Montigny & Aghajanian, 1977; Winter, 1978), have also been shown to act as 5-HT receptor agonists or mixed agonists-antagonists on platelets (Table 1). An exception is psilocybin which in the brain, but not in the platelets, seems to be a 5-HT receptor agonist (Andén, Corrodi & Fuxe, 1971; Everitt & Fuxe, 1977). However, the *in vivo* action of psilocybin may be due to the metabolite psilocine (formed by hydrolysis of the phosphate group in the 4-position) which proved to be a mixed 5-HT agonist-antagonist in platelets. Another possible exception is lisurid, a 5-HT antagonist in platelets which seems to have an agonist action on cerebral 5-HT receptors *in vivo* (Pieri, Schaffner, Pieri, Da Prada & Haefely, 1978).

There are differences in the effects of 5-HT antagonists on various brain areas possibly due to the existence of different types of 5-HT receptors or differences in their affinity for a single receptor type. Major discrepancies exist between drug effects on platelets and the inhibitory 5-HT receptors of those brain areas with a dense 5-HT innervation (raphé nuclei, amygdala, ventral lateral geniculate, optic tectum). In these areas cinanserin, cyproheptadine, methergoline, methysergide, lisurid and methiothepin, which acted as potent 5-HT antagonists in platelets, did not antagonize 5-HT, but rather acted like 5-HT (Born *et al.*, 1972; Drummond & Gordon, 1975; Haigler & Aghajanian, 1977; Kehr 1977; Pieri *et al.*, 1978). In the hippocampus, where the 5-HT terminals have a non-uniform distribution, the 5-HT receptors differed somewhat from those in platelets. Methysergide,

Table 4 Inhibition by methysergide of the platelet shape change induced by various agonists

	Methysergide	
Agonist (M)	IC_{50} (M)	*95% confidence limits*
5-Hydroxytryptamine (10^{-6})	6.2×10^{-9}	5.2–7.5
Truptamine (10^{-6})	4.6×10^{-9}	4.1–5.1
Quipazine (10^{-5})	1.4×10^{-8}	0.9–2.2
Mescaline (10^{-4})	1.0×10^{-8}	0.6–1.6
Adenosine 5'-diphosphate (10^{-6})	$>3 \times 10^{-4}$	

IC_{50} indicates concentration of methysergide inducing 50% inhibition of the maximal shape change caused by the agonist. Mean values of 4–6 experiments.

cyproheptadine LSD and BOL 148 blocked the inhibitory responses to 5-HT whereas cinanserin, mianserin and methiothepin did not exhibit this effect (Segal, 1976; Haigler & Aghajanian, 1977).

The 5-HT receptors of the spinal cord seem to resemble the 5-HT receptors of the platelets more closely. Thus, facilitation of the spinal monosynaptic reflex by the 5-HT precursor 5-hydroxytryptophan and/or the inhibition of the spinal monosynaptic reflex induced by electrical stimulation of the bulbospinal 5-hydroxytryptaminergic pathway (Clineschmidt & Anderson, 1970; Clineschmidt, Pierce & Sjoerdsma, 1971) was antagonized by methysergide, cinanserin, BOL 148, methysergide and (+)-LSD, but not by cyproheptadine. Another type of neurone, i.e. those located in the reticular formation, also seem to react like platelets. The excitatory effect of 5-HT on these neurones was blocked by methysergide, methergoline, cyproheptadine, cinanserin, methiothepin and LSD. However, the excitatory action of 5-HT in the reticular formation has not yet been proven to represent a synaptic effect (Haigler & Aghajanian, 1977).

Finally, some 5-HT receptors of the cerebral cortex seem to show analogies with the platelet receptor. Thus, according to recent findings, neuroleptics interact with 5-hydroxytryptaminergic sites in the cerebral cortex indicating that 5-HT receptors, as well as dopamine receptors, may be involved in the action of these drugs (Leysen, Niemegeers, Tollenafre & Laduron, 1978). Neuroleptics also exhibited strong 5-HT antagonism on platelets. The IC_{50} values for spiroperidol, chlorpromazine and haloperidol were considerably lower than those previously found in PRP (Drummond & Gordon, 1975; Boullin & Glenton, 1978), possibly due to absence of marked protein binding in the present experiments and to species differences. It is of special interest that spiroperidol and methiothepin were among the most potent neuroleptics in interfering with 5-HT receptors and there was high stereoselectivity for D-butaclamol both in brain (Monachon, Burkard, Jalfre & Haefely, 1972; Enna, Bennett, Burt, Creese & Snyder, 1976; Leysen *et al.*, 1978) and in platelets (Boullin & Glenton, 1978).

In conclusion, the 5-HT receptor of the platelet membrane seems to exhibit similarities with certain 5-HT receptors of the CNS (e.g. in spinal cord, cerebral cortex and possibly reticular formation), but not with others (e.g. in amygdala, optic tectum, ventral lateral geniculate, raphé nuclei). A more detailed pharmacological analysis of the CNS as well as comparison of platelets and CNS of the same species are needed in order to substantiate these findings.

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