Human platelet 5-hydroxytryptamine receptors: Binding of [^{3}H]-lysergic acid diethylamide (LSD). Effects of chronic neuroleptic and antidepressant drug administration

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Summary. Chronic treatment with phenothiazines and thioxanthenes has been found to enhance 5-HT-induced aggregation of human platelets. A method has been developed to study 5-HT$_2$ receptor binding sites on platelets utilising [^{3}H]-LSD and more recently ^{125}I/LSD. Results are presented which suggest that the LSD binding site is indeed the 5-HT$_2$ binding site and that the LSD binding characterises the specific receptor responsible for 5-HT-induced shape change and aggregation.
In a group of patients receiving phenothiazines or thioxanthenes, the B_{max} of LSD binding was increased. The mean binding affinity was decreased possibly due to a persistence of neuroleptic in the platelet membrane preparation. Analysis showed that this was not the reason why the mean binding capacity was increased.
The results show that chronic phenothiazine and thioxanthene δ treatment 'up-regulates' platelet 5-HT$_2$ binding sites and that this may be accompanied by increased sensitivity to platelet aggregation by 5-HT.
In normal subjects desipramine treatment increased the B_{max} of platelet LSD binding and this was accompanied by an increased prolactin response to tryptophan which is thought to be mediated by central 5-HT function.
Key words. Platelets; 5-HT; LSD binding; neuroleptics.

The investigations leading to these studies on platelet 5-HT/LSD receptors began following the finding of Mills and Roberts [19] that chlorpromazine and several of its metabolites inhibited in vitro the 5-hydroxytryptamine (5-HT)-induced aggregation of human platelets. This was confirmed by Boullin et al. [4]. It was thought that this inhibition of 5-HT-induced aggregation of human platelets might be used as a pharmacodynamic measure of the effects of neuroleptics in vivo during the treatment of psychotic illness. Surprisingly however, Boullin et al. [5] found that the platelets from many schizophrenic patients treated with chlorpromazine showed enhanced aggregation rather than inhibition of aggregation to 5-HT. This was confirmed for patients treated with fluphenazine [20]. There appeared to be a temporal relationship between changes in platelet aggregation responses and alterations in clinical state [20]. There was some suggestion that enhanced aggregation coincided with clinical improvement and if patients reverted to normal aggregation whilst on neuroleptic agents there was an association with recurrence of schizophrenic symptoms [6, 14].
However, our attempts to replicate these findings were only partially successful [7]. Likewise we were unable to really confirm correlations of enhanced platelet aggregation with clinical state [21]. We were unable to discover whether these discrepancies were due to technical factors in measurement of aggregation, to differences in patient population, or to other factors [15]. However, these early findings of enhanced aggregation in the human were backed up by the findings of Baldacci et al. [3] in the rabbit. They found that chronic treatment of rabbits with chlorpromazine induced increased platelet aggregation responses to 5-HT which began 3–4 days after the start of the chlorpromazine injections and lasted for a similar period when the injections were terminated.
Those of us who were involved in the early investigations on enhanced platelet aggregation to 5-HT in patients undergoing phenothiazine therapy found it difficult to believe that there was not some phenomenon there worthy of further investigation. Because pharmacologically induced adaptive responses are often accompanied by 'up-regulation' or 'down-regulation' of specific receptors, it was decided to try and use radioligand binding techniques to define 5-HT receptors on the human platelet membrane, particularly those mediating 5-HT-induced platelet aggregation. Initially, we used [^{3}H]-5-HT and demonstrated the presence of two separate 5-HT binding sites on intact human platelets, a high affinity site being associated with 5-HT induced aggregation and a low affinity site with 5-HT uptake [24]. The use of [^{3}H]-5-HT as a ligand for two independent sites, proved complicated, particularly as 5-HT is taken up into platelets and endogenous 5-HT can be released from intact platelets and may dilute the ligand [^{3}H]-5-HT during incubation of *intact* platelets.
D-lysergic acid diethylamide (LSD) is a potent inhibitor of 5-HT-induced shape change and aggregation but is inactive against 5-HT uptake in resuspended human platelets [16]. Because [^{3}H]-LSD had been used to label 5-HT receptors in rat brain [2, 22], human brain [10] and rabbit platelets [17] we investigated the binding of [^{3}H]-LSD to human platelet membranes to characterise the specific receptor responsible for 5-HT-induced shaped change and aggregation.
The details of the method were described by Geaney et al. [12]. Essentially, platelet-rich plasma was prepared from venous blood anticoagulated with EDTA. The platelet pellet was prepared, homogenised and the *membrane* pellet prepared by centrifugation. Platelet membranes were used initially for the [^{3}H]-LSD binding assay. Spiperone was used as the displacing agent. Equilibrium binding characteristics of [^{3}H]-LSD were calculated from Scatchard analysis of specific binding data.
The total binding of [^{3}H]-LSD was inhibited by spiperone over approximately two orders of magnitude to reach a plateau at 300 nM spiperone. We therefore used this concentration of spiperone to define a specific binding of [^{3}H]-LSD. Specific binding of [^{3}H]-LSD reached equilibrium by 4 h and remained constant for 10 h at 37 °C. Four hours was chosen as the routine incubation time. When 300 nM spiperone was added, dissociation of the specific binding occurred. The half-time for association was 56 min with an association rate constant of 0.017 ± 0.004 nM$^-$ min$^-$ (mean $K_1 \pm$ SEM). The half-time for dissociation was 173 min with a dissociation rate constant of 0.004 ± 0.0003 min^{-1} (mean $K_2 \pm$ SEM). The equilibrium dissociation constant K_D was 0.24 nM.
The specific binding of [^{3}H]-LSD to human platelet membranes was saturable in the range 0.25–2.5 nM. Scatchard analysis of the binding curve revealed a straight line. Specific binding represented 30%–60% of the total radioactivity bound to the platelet.
Nineteen normal subjects were studied (10 males, 9 females aged 17 to 60 years). The binding affinity (K_D) was 0.53 ± 0.002 nM (mean $\pm$ SEM). The capacity (B_{max}) was 57.1 ± 5.6 fmol/mg protein.
Binding studies in a single male subject repeated on four separate occasions during a 10-day period, showed a coefficient of variation of 16% for the K_D and 11% for the B_{max}.
The specific binding of [^{3}H]-LSD was linearly related to platelet membrane protein concentration in the range 0.05–0.50 mg/ml.

Inhibition studies

Table 1 shows the effects of various antagonists on [^{3}H]-LSD binding to human platelet membranes. Certain 5-HT antagonists were potent inhibitors of the binding. Ketanserin and spiperone (but not dopamine antagonists) were potent inhibitors of [^{3}H]-LSD binding suggesting a 5-HT$_2$ binding site as suggested by Leysen et al.[18]. It is of interest to note that (−)-propranolol was a potent antagonist of LSD binding. Of the endogenous monoamines 5-HT was the most active and 5-HT agonists showed some, but not very marked, activity.

There was no correlation between the ability of substances to inhibit [^{3}H]-LSD binding to human platelet membranes and their inhibition of the active uptake of 5-HT by human platelets (as described by Laubscher and Pletscher[16]). However, there was a highly significant correlation between the inhibition of [^{3}H]-LSD binding and the inhibition of 5-HT induced shape change in suspended human platelets[17]. In addition, there was a close correlation between inhibition of [^{3}H]-LSD binding to human platelet membranes and that to human frontal cortex defined by 1 mmol LSD[12].

The specific binding of [^{3}H]-LSD to platelet membranes was saturable to a site of high affinity, kinetically followed the Law of Mass Action for a biomolecular interaction and demonstrated the specificity and stereo-specificity of a 5-HT receptor. From the agonist and the antagonist studies this binding site correlates with the 5-HT receptor responsible for shape change in aggregation but not that associated with the active uptake of 5-HT and is most likely 5-HT$_2$ in subtype.

The binding of [^{3}H]-LSD to human platelet membranes, occurred slowly reaching equilibrium by 4 h. Dissociation is also slow and thus the affinity calculated by kinetic analysis, is high (K_D = 0.24 nM). The slow rate of association in platelet membranes contrasts with the relatively rapid association of [^{3}H]-LSD to rat cerebral cortical membranes where equilibrium is reached by 10 min at 37 °C[2]. However, there are differences in the concentration of LSD used in the two sets of experiments.

Much of this meeting concerns the pros and cons for use of the platelet as a model for the central 5-HT neurone. The good correlation between [^{3}H]-LSD binding to human platelet membranes and to human frontal cortical membranes supports this analogy.

Table 1. Inhibition of specific binding of [^{3}H]-LSD to human platelet membranes

	IC_{50} nM		IC_{50} nM
5-HT antagonists		Dopamine antagonists	
D-LSD	1.5	Fluphenazine	71.5
Bromo-LSD	2.7	Chlorpromazine	128
Metergoline	2.8	Pimozide	158
Pirenperone	7.3	Haloperidol	1,128
Ketanserin	13.5		
Pizotifen	15.3	β-adrenoceptor antagonists	
Cyproheptadine	23.7	(−)-Propranolol	3,358
Methysergide	30.7	(+)-Propranolol	> 10,000
Endogenous amines		5-HT agonists	
5-HT	185	Quipazine	80.1
Dopamine	> 100,000	5-methoxy-dimethyl-tryptamine	116
Noradrenaline	> 100,000		
5-HT uptake blockers			
Amitriptyline	321		
Fluoxetine	1,256		
Imipramine	1,324		

More recently, we have adapted the method to investigate LSD binding to intact platelets utilising [^{125}I]-LSD. The concentration range of [^{125}I]-LSD from 50 to 150 pM was used. Non-specific binding was defined using spiperone 300 nM. The B_{max} of [^{125}I] LSD binding was 361 ± 47 pmol/10 to 10th platelets. The K_D of LSD binding was 70 ± 14 pM. This compares with the previous [^{3}H]-LSD binding to platelet membranes with a K_D of 240 pM[13].

Effect of chronic neuroleptic treatment on [^{3}H]-LSD platelet binding in schizophrenic patients

Using [^{3}H]-LSD binding to intact platelets, defining a platelet 5-HT$_2$ receptor mediating shape changes and aggregation, we compared platelet 5-HT$_2$ receptor number in groups of schizophrenic patients and matched controls[25]. In-patients and out-patients were studied. All had been diagnosed as schizophrenic. All had been treated with depot neuroleptics (fluphenazine, flupenthixol or clopenthixol as decanoates) for at least 3 months. Concurrent treatment with other neuroleptics, anticholinergics and benzodiazepines was permitted. Fifteen patients were on fluphenazine decanoate, twelve on flupenthixol decanoate and two on clopenthixol decanoate. Thirteen were taking oral neuroleptics, including chlorpromazine, thioridazine, and trifluoperazine. Patients on lithium were excluded.

The control group consisted of normal subjects free of all drugs for at least two weeks with no history of psychiatric illness of migraine. They were well matched for age. The K_D and B_{max} in all groups are shown in table 2. There was a significant increase in the B_{max} of patients on neuroleptics. The statistical significance was greater for the males than for the females.

The mean binding affinity was significantly lower in the patients receiving neuroleptic treatment than in the controls, but this difference did not reach significance for the males or females, separately. The reduction in binding affinity was probably due to a persistence of neuroleptic in the platelet membrane preparation, causing competitive inhibition of the [^{3}H]-LSD binding. Caution has to be exercised in the interpretation of results when changes in both the number of receptors and binding affinity are observed in the study. We excluded an effect of this 'residual' neuroleptic on B_{max} by finding that there was no correlation between the binding capacity and affinity whether analysed as raw data or on logarithmic transformation. Exclusion from analysis of the neuroleptic patients with the lowest affinities such that the result and mean affinity was identical to that of the control group, still resulted in a significant increase in the mean binding capacity in the patients on chronic neuroleptic therapy.

Table 2. Platelet [^{3}H]-LSD binding characteristics in patients on chronic neuroleptic therapy and in controls

	n	B_{max} (fmol/mg protein) (± SEM)	K_D (nM)
Controls			
All	24	57.7 ± 3.7	0.58 ± 0.03
Male	11	54.6 ± 3.1	0.58 ± 0.05
Female	13	60.3 ± 6.3	0.57 ± 0.04
Neuroleptic patients			
All	29	78.5 ± 4.3**	0.69 ± 0.04*
Male	19	75.0 ± 4.4**	0.68 ± 0.05
Female	10	85.1 ± 9.4*	0.71 ± 0.08

* $p < 0.05$ than controls; ** $p < 0.001$ than controls.

There was a positive correlation between [^{3}H]-LSD receptor binding number and total neuroleptic dose expressed as chlorpromazine equivalents ($r = 0.38$, $p < 0.05$).
There is some disagreement as to whether brain 5-HT receptors are 'up-regulated' in animals treated chronically with neuroleptics. Peroutka and Snyder[23] did not find any change in cortical 5-HT$_1$ or 5-HT$_2$ receptor number in rats. On the other hand Dawbarn et al.[11] treated rats for 4–6 months with trifluoperazine and observed intensification of 5-HTP-induced behaviours at the end of this period. In these animals there was an increased number of [3H]-5-HT binding sites in the cortex. These are probably 5-HT$_1$-like binding sites. So the relationship of the human platelet [H^3]-LSD binding (probably 5-HT$_2$) to brain 5-HT receptors is uncertain.
These findings of increased 5-HT aggregability (albeit variable) of human platelets in patients on long-term phenothiazine and thioxanthene drugs, particularly phenothiazines and the 'up-regulation' of platelet 5-HT$_2$ binding sites labelled with [^{3}H]-LSD taken together suggest strongly that phenothiazines and thioxanthene therapy, is associated with an up-regulation of platelet 5-HT$_2$ receptor sites. Whether this is associated with an up-regulation of brain 5-HT receptor sites in the human, is unknown.

How do these changes come about?

There is a tendency to think that receptor number is generally regulated in the long term by the concentration of agonist that a receptor sees. High concentrations might be expected to 'down-regulate' receptors and low concentrations to 'up-regulate' them in order to maintain homeostasis. But how could this apply to the platelet which has no synaptic cleft or mechanism apparent for regulated 'stimulation' by 5-HT? Leaving aside the possibility of internalisation and externalisation of pre-existing receptors in the platelet, the number of receptors on the platelet is determined presumably by gene expression within the megakaryocyte which creates the platelets. If that is the case, why should a neuroleptic such as chlorpromazine cause the megakaryocyte to 'up-regulate' the 5-HT receptors in the platelets which bud off from it? Surely the number of 5-HT receptor sites on the megakaryocyte surface is not determined by the amount of free 5-HT in the plasma flowing through the bone marrow. Nevertheless the timing of changes in platelet receptors would be consistent with changes in platelet population, suggesting that the effect might well be at megakaryocyte level. Another possibility is that the neuroleptics affect gene expression in the megakaryocyte producing 'up-regulation' of 5-HT receptors in the membrane. We have no information on this possibility.

Effect of chronic desipramine treatment on [^{3}H]-LSD binding to platelet membranes of normal subjects

Normal subjects took desipramine hydrochloride, 1.6 to 2.6 mg/kg divided into two daily doses. The total treatment period was 16 days. Seven out of nine patients showed a clear increase in the B_{max} of platelet [^{3}H]-LSD binding. The B_{max} rose from 53 ± 6 to 78 ± 6 fmole/mg platelet protein measured before or on the 16th day of treatment ($p < 0.01$)[9].
In the same study the same normal subjects underwent testing of the prolactin response to tryptophan which is believed to be 5-HT mediated. The prolactin response to tryptophan was enhanced and this enhancement correlated with the increase in platelet [^{3}H]-LSD binding. It is tempting to suggest that desipramine alters not only 5-HT uptake but also 5-HT receptor sensitivity in the platelet and in the brain. However, it is not so simple. The 5-HT receptor on the platelet is of a 5-HT$_2$ sub-type whereas that mediating the tryptophan-induced prolactin response in the brain is more likely to be 5-HT$_1$-like[1, 8]. It would be spurious therefore, to invoke a mechanistic relationship between the increased tryptophan prolactin responses and the increase in platelet 5-HT$_2$ in normal subjects receiving desipramine, however tempting that might be.

Conclusions

Platelets aggregate in response to 5-HT and the site through which the aggregation is mediated can be labelled with [^{3}H] or [^{125}I] LSD and is a 5-HT$_2$ receptor sub-type. It is likely that the second messenger system utilised by the 5-HT$_2$ receptor to initiate platelet aggregation and shape change, is phosphatidylinositol breakdown with second messenger mediation by diacylglycerol and inositol phosphates. The number of LSD receptors on the human platelet can be increased by neuroleptic drug therapy and by desipramine treatment. Whether this reflects changes in brain 5-HT receptors, is unknown at present.

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Platelet research in psychiatry

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Summary. The platelet is one of the most researched biological markers in psychiatry. Characteristics of MAO activity, 5-HT uptake, imipramine and α_2-adrenergic receptor binding, for example, are similar in platelet and CNS. Methodological factors are not negligible, and range from diagnostic specificity and drug effects to the normal physiological variability of age and hormone-related changes, circadian and seasonal rhythms. As yet, there are no clear state or trait platelet markers in affective disorders and schizophrenia that can be unequivocally used to detect vulnerability to the illness, predict therapeutic response, define clinical diagnostic entities or follow the course of the illness. However, platelet markers are increasingly being used in careful studies to monitor psychopharmacological effects (an in vivo assay of all active metabolites), different ligands can be specific markers for certain aspects of a psychiatric illness (e.g. α_2-adrenergic receptors and weight loss), and this homogeneous preparation of human cells is an increasingly important tool in studying mechanisms in pathophysiology. More longitudinal studies are required to establish functional relationships between platelet variables and psychopathology.
Key words. Platelet; psychopathology; MAO activity; 5 HT uptake; imipramine binding; α_2-adrenergic receptors; drug effects.

The search for markers for psychopathology

The serendipitous advent of psychopharmacological agents, and elucidation of the metabolic pathways of the first putative neurotransmitters, resulted in the formulation of precise, testable hypotheses of affective disorders and schizophrenia. Drugs had been found to act on specific symptoms: their modulation of CNS monoamines invoked causal theories. These discoveries led to an entirely new perspective of mental illness – equivalent to a new paradigm – and has shaped the views of clinicians and scientists alike. These discoveries also led to direct measurement of neurotransmitters and their metabolites in man. However, the difficulty of postmortem or cerebrospinal fluid studies, compared with the ease of blood sampling and its possibility of sequential observations, led to the use of different blood cells as possible peripheral representations of central processes. It was the remarkable parallels in a number of properties of the platelet to those in the CNS – the 'neuronal model' concept of Pletscher [82] – that initiated the more dynamic studies in psychiatric illness that will be discussed here. This review does not intend to replicate recent in-depth surveys [21, 33, 49, 58, 73, 82, 93, 101, 102] and makes no pretension to be comprehensive. Instead, I shall adumbrate certain issues that may be critical for an adequate use of platelet markers in psychiatry.

As with post-mortem neurochemistry or CSF metabolites, methodological factors and issues of 'normal' variability were extensively investigated only after the initial flurry of excitement for a new finding was damped by non-replication of the finding by other groups. These methodological factors are not negligible, and additionally, the range of physiologic changes provides important clues to pathophysiology.

Abbreviations: MAO, monoamine oxidase; MAOI, monoamine oxidase inhibitor; 5HT, serotonin; DHE, dihydroergocriptine; cAMP, cyclic adenosine 3′-5′ monophosphate; CNS, central nervous system.

Diagnostic difficulties

The search for markers in psychiatry is perhaps even more desperate than in other fields. In a medical model of mental illness, the brain is the substrate, there is an expectation that some output of the brain can be measured as a differential diagnostic aid, as a predictor for therapeutic response to one or another treatment, and as a monitor of the clinical course of the illness. The difficulties of diagnosis need to be explicitly recognised in research on biological markers, since homogeneity of patient populations is a prerequisite for specificity:

- conceptual: disease model or spectrum model?
- descriptive or diagnostic language with aetiological implications (e.g. 'endogenous' vs 'neurotic' depression)
- the distinction between 'trait' and 'state' markers
- the phase of the illness studied