The Binding of Phytohemagglutinins to Human Platelet Plasma Membranes*

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SUMMARY

The binding of phytohemagglutinins from Phaseolus vulgaris (erythroagglutinating phytohemagglutinin (E-PHA) and leukoagglutinating phytohemagglutinin (L-PHA)) and from Lens culinaris (lentil-PHA) to human platelet cell surfaces has been demonstrated. Each platelet binds on an average 500,000 to 600,000 molecules of E-PHA with an apparent dissociation constant of 0.5 \times 10^{-7} M. These values were 250,000 to 350,000 molecules bound for L-PHA and 300,000 to 400,000 molecules bound for lentil-PHA with dissociation constants of 4 \times 10^{-7} M and 1.4 \times 10^{-7} M, respectively. Both E-PHA and lentil-PHA can be released from the platelet surface using appropriate oligosaccharide hapten inhibitors, indicating that the phytohemagglutinins do not enter the cells. When E-PHA and L-PHA bind to platelets the cells are aggregated, adenylate cyclase is inhibited, and a protein designated as thrombin-sensitive protein is released from the particulate fraction of the cell. Thus, binding of these compounds to the platelet surface mimics thrombin-induced aggregation and the release reaction. Lentil-PHA binds tightly to platelets but the cells do not aggregate and there is no inhibition of adenylate cyclase or release of thrombin-sensitive protein. Thrombin induces platelet aggregation, adenylate cyclase inhibition, and thrombin-sensitive protein release even when platelets are saturated with lentil-PHA. After incubation of platelets with either thrombin or L-PHA, there is an apparent 2-fold increase in the number of receptor sites for lentil-PHA, suggesting that these compounds produce a conformational change in the platelet surface exposing increased numbers of lentil-PHA receptor sites.

Many of these compounds are mitogenic for lymphocytes and differences in the binding of phytohemagglutinins between normal and chronic lymphocytic leukemia lymphocytes have been demonstrated (4). Chronic lymphocytic leukemia lymphocytes have decreased numbers of surface receptors for the phytohemagglutinins from P. vulgaris (erythroagglutinating phytohemagglutinin and leukoagglutinating phytohemagglutinin), and they also show a delayed and decreased mitogenic response as compared with normal lymphocytes (5). Other studies have shown that tumor cells are more easily agglutinated than normal cells by wheat germ agglutinin, concanavalin A, and other phytohemagglutinins (3, 6). Recent studies suggest that the differences between agglutinability of normal and malignant or transformed cells relates to differences in either the conformation or distribution of receptor sites on the cell surface rather than to actual differences in the numbers of binding sites (7-9). The phytohemagglutinins bind to carbohydrate structures on the cell surface and exert their mitogenic effect while external to the cell itself (10).

We have studied the interactions between intact human platelets and three phytohemagglutinins, all of which are mitogenic for lymphocytes. These include E-PHA, L-PHA, and the phytohemagglutinin isolated from lentils. Human platelets have been shown to have large numbers of surface receptors for each of these compounds. In other studies we have analyzed the effects of these phytohemagglutinins on cell functions especially components of the platelet release reaction.

METHODS

Human platelets were collected, isolated, and washed as described previously (11, 12). All experiments were conducted within 2 to 6 hours of initial blood collection. E-PHA and L-PHA were isolated from Difeo phytohemagglutinin P by the method of Weber et al. (13). Lentil-PHA was isolated from dried lentils obtained from a local grocer by the method of Howard et al. (14) as modified by Kornfeld et al. (2). This purification results in the isolation of two phytohemagglutinins which are identical both in terms of erythrocyte binding and mitogenicity for lymphocytes. Lentil B (14) was used in all studies reported in this paper. The concentration of all phytohemagglutinins solutions was estimated by measuring the ab-
volume of 0.5 ml of isotonic Tris-0.87% NaCl solution buffer previously soaked overnight in 0.5 ml bovine serum albumin. Reaction mixtures contained 0.5 to 2 mg of phytohemagglutinin in 1 ml of 0.1 M potassium phosphate buffer, pH 7.7. After addition of 20 to 200 μCi of radioactive sodium iodide, chloramine-T (0.4 mg in 0.1 ml) was added to the reaction mixture. Iodination reactions were stopped by addition of 0.10 ml of sodium metabisulfite (2.4 mg per ml) after 5 to 10 s. These short periods of iodination prevented denaturation of the phytohemagglutinins by chloramine-T. The labeled phytohemagglutinins were then separated from free iodide by filtration through a column of Sephadex G-25. The phytohemagglutinins were then stored at -20°C and were stable for several months. γG-glycopeptide (M-M) (18) and fetuin glycopeptide were gifts from Dr. Stuart Kornfeld.

Iodination of Phytohemagglutinins—Homogeneous phytohemagglutinins were iodinated with either [131I]- or [125I]-sodium iodide purchased from Mallinckrodt Nuclear Co. using the chloramine-T method of Hunter (17). Reaction mixtures contained 0.5 to 2 mg of phytohemagglutinin in 1 ml of 0.1 M potassium phosphate buffer, pH 7.7. After addition of 20 to 200 μCi of radioactive sodium iodide, chloramine-T (0.4 mg in 0.1 ml) was added to the reaction mixture. Iodination reactions were stopped by addition of 0.10 ml of sodium metabisulfite (2.4 mg per ml) after 5 to 10 s. These short periods of iodination prevented denaturation of the phytohemagglutinins by chloramine-T. The labeled phytohemagglutinins were then separated from free iodide by filtration through a column of Sephadex G-25. The phytohemagglutinins were then stored at -20°C and were stable for several months. γG-glycopeptide (M-M) (18) and fetuin glycopeptide were gifts from Dr. Stuart Kornfeld.

Phytohemagglutinin Binding Studies—Reactions were carried out in plastic Falcon tubes (12 × 75 mm) which had been previously soaked overnight in 0.5% bovine serum albumin. Reaction mixtures contained 5 × 10⁷ platelets, phytohemagglutinin (0.1 to 100 μg), or other additions where indicated, in a final volume of 0.5 ml of isotonic Tris-0.8% NaCl solution buffer (0.14 M NaCl containing 0.0154 M Tris-HCl, pH 7.4, with 1 mg per ml of glucose). After incubation for 30 min at room temperature with occasional mixing, 4 ml of cold (0°C) Tris-saline was added and the mixture was filtered through a Millipore filter (either 0.45- or 1.2-μm filters) using a siliconized Millipore filter apparatus. The filters were washed with 10 ml of cold Tris-saline and were then counted in a Packard autogamma counter. Background values were obtained from incubations in which platelets were omitted. The Millipore filters used in these experiments were soaked in 0.5% bovine serum albumin overnight prior to use. In some experiments the platelets were collected by centrifugation at 1000 × g for 15 min at 4°C after addition of cold Tris-saline and the platelet pellets were counted directly in the autogamma counter.

RESULTS

In order to perform valid binding studies with radio-iodinated phytohemagglutinins, two conditions must be met. First, the phytohemagglutinin must be free of contaminating proteins so that the specific radioactivity of the phytohemagglutinin can be used to calculate the amount bound to the cell. Thus, if contaminating proteins were iodinated but cannot bind, the specific radioactivity estimate would be in error. Secondly, it is essential that the radioactive phytohemagglutinin not be denatured by the iodination process in order to avoid errors in measurements of the affinity of binding and the number of binding sites per cell. The E-PHA, L-PHA, and lentil-PHA preparations used in these experiments were all homogeneous as judged by both disc gel electrophoresis and by electrophoresis in sodium dodecyl sulfate-polyacrylamide gels. Furthermore, the agglutinating activity of both E-PHA and lentil-PHA for erythrocytes was identical whether radio-iodinated or unlabeled preparations were used.

In preliminary experiments it was shown that all three phytohemagglutinins tested did bind to platelets. The time required for binding to reach equilibrium at 25°C was 15 to 20 min and for all subsequent experiments 30-min incubations were used. The plastic Falcon tubes and Millipore filters used in these experiments were soaked in 0.5% bovine serum albumin prior to use to prevent nonspecific adsorption of labeled phytohemagglutinin. When this was done the background radioactivity was always <5% of that found in the presence of platelets. Similar binding data were obtained using either the Millipore filtration technique or the centrifugation technique to collect the platelets. There was no significant loss of bound phytohemagglutinin even after extensive Tris-saline washing of platelets.

The binding of E-PHA, L-PHA, and lentil-PHA to platelets is shown in Fig. 1. These curves show saturation kinetic data similar to those found in studies of binding of phytohemagglutinins to erythrocytes (2) and Erhlich ascites tumor cells (19). These results are plotted according to the method of Steck and Wallach (19) in Fig. 2. Using this technique the intercept on the ordinate is a measure of the number of sites for phytohemagglutinin on the platelet surface while the intercept on the abscissa is a measure of the affinity of the platelet for phytohemagglutinin. From a number of experiments these values were 250,000 to 350,000 sites per platelet for L-PHA with an apparent dissociation constant of 4 × 10⁻⁷ M. For E-PHA the values were 500,000 to 600,000 sites per platelet with a dissociation constant of 0.5 × 10⁻⁷ M, and for lentil-PHA there were 300,000 to 400,000 sites per platelet with an apparent dissociation constant of 1.4 × 10⁻⁷ M. These values are only relative approximations since the calculated values assume that each molecule of phytohemagglutinin binds to a single site on the platelet. In fact the phytohemagglutinins have at least two binding sites per molecule and thus the number of sites per platelet given here are minimum estimates and the dissociation constants are maximum estimates. Evidence that the iodination procedure did not denature the phytohemagglutinins was obtained from the finding that when unlabeled phytohemagglutinin was added in a constant amount to each tube in a binding reaction there was competitive inhibition of binding and the calculated Kᵰ of unlabeled phytohemag-

Fig. 1. Binding of phytohemagglutinins to platelets. Platelets were incubated with [131I]-labeled phytohemagglutinins and binding was measured as described in "Methods." The concentration of PHA was calculated assuming a molecular weight of 90,000 for lentil-PHA (14) and 128,000 for E-PHA and L-PHA (13). ●—●, L-PHA; ○—○, lentil-PHA; ▲—▲, E-PHA.
has no effect on E-PHA or L-PHA binding to platelets at the
cell suspension was further incubated 10 min to allow lentil-PHA
agglutination by lentil-PHA. After incubation of platelets with
lentil-PHA, an excess of γG-glycopeptide was added and the
agglutination was measured as described in “Methods” (O-O). The
γG glycopeptide solution used was 4.5 X 10^-3 M and was added to
give the final concentrations noted above.

### Table I

<table>
<thead>
<tr>
<th>γG-glycopeptide added</th>
<th>Thrombin</th>
<th>Lentil PHA bound</th>
<th>Lentil-PHA released</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 M</td>
<td>1 unit/ml</td>
<td>mg</td>
<td>%</td>
</tr>
<tr>
<td>1.2</td>
<td>0.62</td>
<td>0.29</td>
<td>44</td>
</tr>
<tr>
<td>2.4</td>
<td>0.145</td>
<td>0.041</td>
<td>62</td>
</tr>
<tr>
<td>7.9</td>
<td>0.041</td>
<td>0.022</td>
<td>92</td>
</tr>
<tr>
<td>15.8</td>
<td>0.72</td>
<td>0.04</td>
<td>95</td>
</tr>
</tbody>
</table>

Fig. 2. Binding of phytohemagglutinin to platelets plotted
by the method of Steck and Wallach (19) according to the equation

\[
\frac{[\text{PHA bound}]}{[\text{PHA}]} = \frac{1}{K \cdot n} + \frac{1}{n}
\]

where PHA = concentration of free PHA, n = number of PHA
binding sites per platelet, platelet = number of platelets per
eraction mixture, and K is the affinity constant of PHA. •-•,
L-PHA; ○-○, lentil-PHA; △-△, E-PHA.

Clotting was equal to the dissociation constant obtained using
the corresponding labeled compounds.

**Removal of Bound Phytohemagglutinin from Platelet Surface**

It was necessary to establish that the phytohemagglutinins bind
to the platelet surface and do not enter the cells in order for these
binding studies to be valid. Therefore, we attempted to remove
bound phytohemagglutinin from the platelet surface using known
haptene inhibitors of the various phytohemagglutinins. Korn-
feld et al. (18) have isolated a glycopeptide from a γG-myeloma
protein (M-M) which is a potent haptene inhibitor of erythrocyte
agglutination by lentil-PHA. After incubation of platelets with
lentil-PHA, an excess of γG glycopeptide was added and the
cell suspension was further incubated 10 min to allow lentil-
PHA to exchange off the platelet surface. The results of this
experiment are shown in Table I. At high concentrations of
γG-glycopeptide over 95% of lentil-PHA was removed. Fur-
thermore, the binding curve for lentil-PHA in the presence of
γG-glycopeptide (Fig. 3) shows competitive inhibition between
the glycopeptide and the platelet surface receptors suggesting
that the glycopeptide acts as a haptene inhibitor of binding and
was not directly toxic to the platelets. The γG-glycopeptide
has no effect on E-PHA or L-PHA binding to platelets at the
concentrations tested. A glycopeptide isolated from fetuin has
haptene inhibitory activity toward E-PHA erythrocyte agglu-
tination (1). When 8 X 10^-4 M fetuin glycopeptide was incubated
with platelets after E-PHA was bound (0.62 X 10^6 molecules
per platelet) 88% of the E-PHA was removed from the platelet
surface. While there is no known haptene inhibitor for L-PHA,
it is likely that it also binds almost solely to the platelet surface.

**Effects of Phytohemagglutinin on Platelet Release Reaction**—In
experiments in which binding of E-PHA and L-PHA to platelets
was measured there was marked agglutination of platelets at
concentrations which approximate the association constants for
these compounds. There was no apparent agglutination of
platelets when lentil-PHA was used, although, if lentil-PHA-
saturated platelets were collected by centrifugation, they did
aggregate when pelleted. Since E-PHA and L-PHA were capa-
ble of aggregating platelets it was of interest to determine
whether these compounds could produce any phenomena of the
platelet release reaction. This reaction occurs in the process of
hemostasis and is characterized by the rapid release of platelet
adenine nucleotides, serotonin, sulfated mucopolysaccharides,
and specific proteins (12). Previous studies from several labora-
tories have indicated that platelets contain adenylate cyclase
(19 to 24). Compounds which affect the activity of this enzyme
and as a result the concentrations of adenosine 3',5'-monophos-
phate in platelets have marked effects on platelet aggregation
and the release reaction. Thus agents which decrease adenylyl
cyclase activity produce aggregation and induce the platelet
release reaction (23, 24). Recently we have demonstrated that
thrombin-induced platelet aggregation and release are associated
with a rapid inactivation of the membrane enzyme adenylate

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**Fig. 3.** Release of lentil-PHA from platelets. Lentil-PHA
binding was measured as described in "Methods" (O-O). γG-glycopeptide (2.7 X 10^-5 M) was added after incubation of
platelets with lentil-PHA for 30 min and after an additional 10-
minute incubation the plates were collected and lentil-PHA bind-
ing was measured •-•.
could reflect a change in the surface conformation of the platelet. Thus, if the affinity of the platelet or the number of binding sites for lentil-PHA were affected by thrombin it did not interfere with the thrombin reaction suggested the possibility of using lentil-PHA as a probe of the surface conformation of the platelet. The fact that binding of lentil-PHA to the platelet surface inactivation of adenylate cyclase and release of the thrombin-sensitive protein was demonstrated using three different phytohemagglutinins. The apparent numbers of available surface receptors and could be released by the haptene glycopeptide. Since the receptors for lentil-PHA are on oligosaccharide chains of the cell surface (2), and since in other cells these receptors appear to be widely distributed over the plasma membrane (9, 25), these results suggest that thrombin induces a change in the gross conformation of the cell surface. In experiments with L-PHA-induced agglutination of platelets, a similar result was obtained with approximately a 2-fold increase in the apparent number of binding sites for lentil-PHA.

When platelets were incubated with E-PHA at 100 μg per ml there was a lesser but clear inhibition of adenylate cyclase and parallel release of thrombin-sensitive protein. This amount of E-PHA was sufficient to aggregate the platelets and to saturate approximately 4 of the sites on the platelet surface. Similar results were obtained using L-PHA. When lentil-PHA was used there was no release of thrombin-sensitive protein or inactivation of adenylate cyclase even when the platelet receptors were saturated (and the platelets did not aggregate). Despite saturation of the platelet receptors with lentil-PHA, thrombin-induced inactivation of adenylate cyclase and release of thrombin-sensitive protein still occurred.

Effect of Thrombin Treatment of Platelets on Binding of Lentil-PHA—The fact that binding of lentil-PHA to the platelet surface did not interfere with the thrombin reaction suggested the possibility of using lentil-PHA as a probe of the surface conformation of the platelet. Thus, if the affinity of the platelet or the number of binding sites for lentil-PHA were affected by thrombin it could reflect a change in the surface conformation of the platelet.

### Table II

<table>
<thead>
<tr>
<th>Additions</th>
<th>Thrombin-sensitive protein</th>
<th>Adenylate cyclase activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>units b</td>
<td>% released</td>
</tr>
<tr>
<td>1. None</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td>2. Thrombin 1 unit per ml</td>
<td>2.8</td>
<td>81</td>
</tr>
<tr>
<td>3. E-PHA, 0.1 μg per ml</td>
<td>0.3</td>
<td>65</td>
</tr>
<tr>
<td>4. Lentil-PHA, 0.1 mg per ml</td>
<td>14.2</td>
<td>5</td>
</tr>
<tr>
<td>5. Lentil-PHA, 0.1 mg per ml, plus thrombin, 1 unit per ml</td>
<td>0.0</td>
<td>60</td>
</tr>
</tbody>
</table>

* Adenosine 3′, 5′ monophosphate.

a One unit of thrombin-sensitive protein corresponds to about 1 μg of protein as determined by densitometry of SDS-polyacrylamide gels containing 200 μg of membrane protein (15).

The results of this experiment are shown in Fig. 4. In these experiments to lentil-PHA and thrombin were mixed and the reactions were started by addition of platelets. Thrombin caused approximately a 2-fold increase in the apparent number of binding sites for lentil-PHA on the platelet surface. This increase could not be accounted for by trapped lentil-PHA in the platelet aggregate as the volume of the aggregate could only trap about 1% of the increased lentil-PHA bound. The increased lentil-PHA bound after thrombin was also released by subsequent incubation with γG-glycopeptide as shown in Table I indicating that lentil-PHA was actually bound to increased numbers of available surface receptors and could be released by the haptene glycopeptide. Since the receptors for lentil-PHA are on oligosaccharide chains of the cell surface (2), and since in other cells these receptors appear to be widely distributed over the plasma membrane (9, 25), these results suggest that thrombin induces a change in the gross conformation of the cell surface. In experiments with L-PHA-induced agglutination of platelets, a similar result was obtained with approximately a 2-fold increase in the apparent number of binding sites for lentil-PHA.

**DISCUSSION**

Previous studies have demonstrated binding of various phytohemagglutinins to a variety of normal and malignant cells. Binding is often associated with marked functional effects. Thus, lymphocytes are converted from resting cells to dividing cells. Burger and Noonan (26) have shown that binding of monoclonal concanavalin A to the surface of tumor cells restores the property of contact initiation of growth. In this study we have demonstrated binding of high affinity to human platelets using three different phytohemagglutinins. The apparent number of sites on platelets for phytohemagglutinin binding is comparable to that found on lymphocytes per unit surface area (3). Binding of both E-PHA and L-PHA has striking functional effects on the platelet. These compounds cause platelet aggregation, inhibition of adenylate cyclase, and release of thrombin-sensitive protein. Preliminary experiments indicate that these compounds also produce nucleotide and serotonin release. The

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**FIG. 4.** Effect of thrombin on lentil-PHA binding. Lentil-PHA binding to platelets was measured in the presence and absence of thrombin, 1 unit per ml, as described in "Methods." Reactions were started by the addition of platelets. ○—○, lentil-PHA; ○—○, lentil-PHA + thrombin.

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time course of the phytohemagglutinin reaction is markedly
different than thrombin-induced release. Release occurs within
15 s using thrombin (1 unit per ml); while the phytohemagglu-
tinin reactions proceed much slower only after binding has
occurred (5 to 10 min).

The finding that these proteins from plants bind tightly to
surface receptors on a wide variety of cells to produce different
physiological effects suggests that the possibility that high affinity
binding of relatively large numbers of ligand molecules to a cell
surface may trigger physiological functions which vary with cell
type. It is not clear whether the phytohemagglutinins bind to
cell surfaces monovalently or bivalently. Bivalent binding
(either between cells or on one cell) might explain the apparent
low dissociation constants for these compounds. Thus, the
phytohemagglutinin is freed from the cell surface only when both
binding sites dissociate from the cell surface simultaneously.
This could explain the loss of cell surface phytohemagglutinins
with haptenic ligands (γG-glycopeptide, fetuin glycopeptide)
while extensive washing fails to remove them. This hypothesis
can be tested only by preparing monovalent phytohemagglutinins
and demonstrating markedly decreased affinities for binding to
cell surfaces while binding to monovalent haptenes remains
unchanged. It would then be of interest to determine the
physiological effects of such monovalent phytohemagglutinins.
Apparently the thrombin induced platelet release reaction is
mediated through inhibition of adenylate cyclase. Binding of
E-PHA to platelets leads to inhibition of adenylate cyclase while
E-PHA binding to lymphocytes has been reported to increase
lymphocyte adenosine 3',5'-monophosphate (27). Thus, the
physiological effects of phytohemagglutinin binding to different
cells may be mediated in part through the adenosine 3',5'-mono-
phosphate system (28).

Lentil-PHA was found to bind tightly to platelets but this
binding was not associated with any release of thrombin-sensi-
tive protein or inhibition of adenylate cyclase. Platelets satu-
rated with lentil-PHA still responded normally to thrombin thus
allowing for use of lentil-PHA as a conformational probe of the
platelet surface. That thrombin causes a marked change in the
surface conformation of the platelet is suggested by the apparent
2-fold increase in the number of sites for lentil-PHA binding per
platelet. A similar increase in the number of lentil-PHA sites
was observed when L-PHA was added to platelets, thus suggest-
ing that L-PHA and thrombin produce a similar conformational
change in the platelet surface.

We have previously assumed that thrombin acts by some
proteolytic action on a platelet surface substrate. The finding
that the action of thrombin can be mimicked by binding of
phytohemagglutinin raises the possibility that proteolysis might
not be involved in the action of thrombin. Further study of
thrombin action on platelets is required to settle this question.

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