Disparate effects of the calcium-channel blockers, nifedipine and verapamil, on α₂-adrenergic receptors and thromboxane A₂–induced aggregation of human platelets

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ABSTRACT Calcium-channel blockers inhibit human platelet aggregation in vitro and ex vivo. To further evaluate the mechanism(s) responsible for the inhibition induced by this structurally heterogeneous group of compounds, we studied the effect of nifedipine and verapamil on human platelet aggregation in vitro. Neither 10 μM nifedipine nor 10 μM verapamil consistently inhibited the aggregation response of platelet-rich plasma to threshold concentrations of ADP, sodium arachidonate, epinephrine, or collagen. However, both 10 μM nifedipine and 10 μM verapamil inhibited epinephrine-potentiated, thromboxane A₂ (TXA₂)–induced aggregation of aspirin-incubated, gel-filtered platelets. Aggregation of similarly prepared platelets induced by TXA₂ alone was abolished by 10 μM nifedipine but not by 10 μM verapamil. Even 100 μM verapamil gave only partial and inconsistent inhibition of aggregation. Both drugs had essentially the same effects on platelet aggregation induced by the stable endoperoxide and TXA₂ mimic, U46619, with or without epinephrine. Neither 10 μM nifedipine nor 10 μM verapamil elevated platelet cyclic AMP. Verapamil (10 μM) inhibited binding of [³H]yohimbine (an α₂-adrenergic receptor antagonist) to intact human platelets (Kᵢ 10.5 nM vs 2.4 nM for control platelets) without altering the number of binding sites. In contrast, 10 μM nifedipine had no effect on Kᵢ or number of binding sites. These results indicate that nifedipine and verapamil inhibit epinephrine-potentiated, TXA₂–induced human platelet aggregation by different mechanisms. Verapamil inhibits the epinephrine contribution to the aggregation response by blocking α₂-adrenergic receptor binding. Nifedipine blocks the platelet response to TXA₂ without affecting α-adrenergic receptor binding. These observations have potential clinical implications with regard to the mechanisms by which calcium-channel blockers inhibit vascular spasm and myocardial ischemia.


THE CALCIUM-CHANNEL BLOCKERS are a heterogeneous group of drugs that share the common characteristic of inhibiting the influx of calcium ions across the plasma membranes of excitable cells.¹-³ These drugs inhibit human platelet aggregation in vitro₄-²¹ and ex vivo.⁸, 9, 22-24 Two calcium-channel blockers whose platelet inhibitory properties have been studied by several investigators are nifedipine and verapamil. They have been found to have different effects on platelets. At minimum inhibitory concentrations, verapamil preferentially inhibits epinephrine-induced platelet aggregation⁵, ⁸, ₁₂, ₁₃, ₁₈ by competitively binding to α₂-adrenergic receptors,¹₃, ₁₄ whereas at comparable concentrations nifedipine also inhibits platelet aggregation induced by other agonists.⁵, ⁹

Previous investigations of the effect of the calcium-channel blockers on platelet aggregation suggested inhibition of thromboxane A₂ (TXA₂)–mediated events. Both nifedipine and verapamil inhibited the secondary (TXA₂-dependent) wave of ADP-induced platelet aggregation at concentrations lower than those required to inhibit the primary (TXA₂-independent) wave.⁶, ⁸, ⁹, ₁₁, ₁₈ Formation of thromboxane B₂ (TXB₂), the stable, inactive hydration product of TXA₂, was inhibited by nifedipine or verapamil in platelets stimulated by a variety of agonists.¹₀-₁₂, ₁₈, ₁₉ However, several inconsistencies in the data raised questions regarding the significance of inhibition of platelet TXB₂ formation.¹₀, ₁₈, ₂¹ Therefore we investigated an alterna-
tive mechanism by which calcium-channel blockers could inhibit TXA2-mediated events, i.e., inhibition of the platelet response to TXA2. We studied the effect of nifedipine or verapamil on platelets stimulated by TXA2 or the stable endoperoxide analog and TXA2 mimic, U46619,25 in the presence or absence of epinephrine. The results of this study indicate that nifedipine and verapamil inhibit epinephrine-potentiated, TXA2-induced human platelet aggregation by different mechanisms.

Methods

Twelve healthy adult subjects who had taken no medication during the previous week were studied. Written informed consent was obtained from each subject for participation in a study approved by the Human Subjects Subcommitte of the Minneapolis Veterans Administration Medical Center. Blood was drawn from an antecubital vein by a two-syringe technique and immediately mixed with 3.8% sodium citrate (9 vol:1 vol) in plastic tubes. Sodium citrate-anticoagulated platelet-rich plasma (C-PRP) was prepared by centrifuging at 800 g for 10 min. Platelet-poor plasma was obtained by further centrifugation at 1500 g for 30 min. Verapamil, a gift from Knoll Pharmaceutical Co., was prepared in a stock solution of 1 mM in saline. Nifedipine, a gift from Pfizer Laboratories, was prepared in a stock solution of 1 mM in ethanol. U46619 was obtained from the Upjohn Co., Kalamazoo, MI.

Aggregation of human C-PRP. The aggregation responses of C-PRP to minimum concentrations of ADP (1.25 to 2.5 μM), sodium arachidonate (0.33 to 0.66 mM), epinephrine (0.54 to 5.4 μM), and acid-soluble bovine collagen (0.2 to 0.6 μg/ml) were observed before and after incubation of C-PRP with nifedipine, verapamil, or ethanol for 3 min. Because alcohol inhibits platelet aggregation, when added directly to gel-filtered platelets, the appropriate volume of nifedipine in alcohol was added to the aggregation cuvette and the alcohol evaporated before the addition of the gel-filtered platelets. The concentrations of nifedipine cited are the concentrations in alcohol added to the cuvette before evaporation. The final concentrations achieved were likely lower.

Aggregation of human gel-filtered platelets induced by TXA2 or U46619. Human platelets were separated from plasma by filtration through Sepharose 2B columns. The columns were eluted with modified Lindon’s buffer.26 Gel-filtered human platelets were incubated with aspirin to block TXA2 formation and stirred at 37°C in an aggregometer. Nonaggregating dog C-PRP was used as a source of TXA2, as described by Charo et al.27 and modified in our laboratory.28,29 Only conditioned dogs whose platelets consistently failed to aggregate or secrete on repetitive testing performed over a period of 1 to 4 years were used as a source of TXA2. Sodium arachidonate (0.33 mM) was added to 0.5 ml of dog C-PRP and stirred in an aggregometer. One minute after the addition of arachidonate, a 15 to 30 μl aliquot was removed from the stirred dog C-PRP and transferred to gel-filtered, aspirin-incubated human platelets stirred in a second aggregometer cuvette. The gel-filtered platelets were studied at a cell count of 200 to 300,000/μl. Platelets prepared in this fashion from normal humans aggregated promptly and secreted 14C-serotonin and ATP in response to TXA2.28,29 Human gel-filtered, aspirin-incubated platelets were incubated with verapamil or nifedipine (1 to 100 μM), ethanol, or buffer for 5 min before the addition of the aliquot of dog platelets containing TXA2. Simultaneous control experiments were performed with each drug experiment. Subaggregating quantities of TXA2 resulted in irreversible aggregation of human platelets when subaggregating concentrations of epinephrine were added before TXA2.

To verify the interpretation that the platelet aggregating activity of dog platelets stirred with sodium arachidonate was attributable to TXA2, the response of gel-filtered human platelets to U46619 was also evaluated. The minimum concentration of U46619 that induced irreversible platelet aggregation was determined for each experiment. The pattern of response to U46619 was equivalent to that induced by TXA2 formed by dog platelets.

Human C-PRP cyclic AMP. The cyclic AMP activity of human C-PRP in the presence of 10 μM nifedipine, 10 μM verapamil, or ethanol was measured by radioimmunoassay as previously described.28

Human platelet binding of [3H]-yohimbine. α2-Adrenergic receptors were quantified with the selective α2-receptor agonist, [3H]-yohimbine, by a method previously described.30 Platelets were separated from plasma and washed twice in a washing buffer (0.67 g/liter KH2PO4, 5.52 g/liter NaH2PO4, H2O, 6.0 g/liter NaCl, 1.0 g/liter dextrose, 2.0 g/liter disodium EDTA, pH 7.6) by centrifugation and gentle resuspension of pellets at 5°C. The final washed platelet pellet was gently resuspended in an incubation buffer (50 mM TRIS, 100 mM NaCl, 5 mM EDTA, pH 7.4). The volume of the incubation buffer was adjusted to give a final platelet concentration of 4 to 10 × 10^10/μl. The final platelet concentration was determined by counting aliquots in triplicate in a Coulter counter after gentle mixing. The platelet count and freedom from microaggregates were verified by direct observation in a hemacytometer under phase-contrast microscopy.

To determine ligand binding, duplicate 200 μl aliquots of washed platelet suspension were incubated with 25 μl of various concentrations (0.2 to 10 nM) of [3H]-yohimbine (New England Nuclear, 89.7 Ci/mmol) in polypropylene tubes for 50 min at 37°C. At the end of the incubation period, samples were diluted with 4 ml of the incubation buffer, passed over glass fiber filters (Whatman GF/A), and washed with an additional 20 ml of buffer. The radioactivity retained by the filters was determined by liquid scintillation counting. Nonspecific binding was determined by parallel treatment of duplicate samples in incubation buffer containing 10 μM phentolamine. Specific binding was defined as total binding minus nonspecific binding. Scatchard analysis of the binding data yielded the dissociation constant (Kd) and maximum receptor binding (Bmax), the maximum number of receptors per platelet. The mean correlation coefficient for the Scatchard plots was 0.92 ± 0.11 (mean ± 1 SD; n = 44). Adrenergic receptor assays were performed on platelets from nine control subjects (four women, five men). The range of Kd and receptor number varied from 1.5 to 5.0 and from 120 to 268, respectively. In one subject five repeat determinations revealed a range of receptor number from 195 to 257. These values are within the range reported for this method.30,31

Statistical methods. Equilibrium binding was analyzed by Scatchard plots.32 Kd and receptor number were calculated as previously described.13,14,30 Values are expressed as mean ± SD. Correlation coefficients and standard deviations were calculated by standard methods.33 The significance of differences between means was determined by Student’s t test for paired or unpaired data.33

Results

Aggregation of human C-PRP. Neither 10 μM nifedipine nor 10 μM verapamil consistently inhibited aggregation of human C-PRP induced by sodium arachidonate, ADP, collagen, or epinephrine (table 1).
Aggregation of human gel-filtered platelets induced by TXA₂ or U46619. Nifedipine (10 μM) consistently abolished aggregation of aspirin-incubated, gel-filtered platelets induced by a subaggregating quantity of TXA₂ plus a subaggregating concentration of epinephrine (usually 0.54 μM) (table 2, figure 1). Epinephrine-potentiated, TXA₂-induced platelet aggregation was also markedly inhibited by 10 μM verapamil in most studies (table 2, figure 1). At lower concentrations, verapamil more frequently inhibited the aggregation response than did nifedipine (table 2).

Aggregation of aspirin-incubated, gel-filtered human platelets induced by TXA₂ alone was consistently abolished by 10 μM nifedipine (table 3, figure 2). Verapamil was not significantly inhibitory under the same conditions even at 100 μM (table 3, figure 2).

The effect of nifedipine and verapamil on platelet aggregation induced by U46619 was essentially the same as the effect of these drugs on TXA₂-induced aggregation. Substantial inhibition of epinephrine-potentiated, U46619-induced platelet aggregation was observed with 10 μM or greater verapamil or 2.9 μM or greater nifedipine (figure 3). Marked inhibition of aggregation induced by U46619 alone was also observed with 2.9 μM or greater nifedipine, but 100 μM verapamil had no inhibitory effect (figure 4).

**TABLE 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Arachidonate</th>
<th>ADP</th>
<th>Collagen</th>
<th>Epinephrine</th>
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<tr>
<td>Nifedipine (10 μM)</td>
<td>63 ± 48B (33)C</td>
<td>9</td>
<td>84 ± 16 (0)</td>
<td>67 ± 22 (23)</td>
</tr>
<tr>
<td>Verapamil (10 μM)</td>
<td>78 ± 36 (15)</td>
<td>13</td>
<td>79 ± 20 (13)</td>
<td>72 ± 25 (25)</td>
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A Number of studies.
B% of simultaneous control aggregation (mean ± SD). Data from study of six normal subjects.
C% of studies with aggregation < 50% of control.

**TABLE 2**

<table>
<thead>
<tr>
<th>Drug</th>
<th>10 μM</th>
<th>1 μM</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No. studies</td>
<td>% Studies &lt;50% of control</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>15</td>
<td>93</td>
</tr>
<tr>
<td>Verapamil</td>
<td>13</td>
<td>69</td>
</tr>
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</table>

**TABLE 3**

<table>
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<tr>
<th>Drug</th>
<th>100 μM</th>
<th>10 μM</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No. studies</td>
<td>% Studies &lt;50% of control</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>Verapamil</td>
<td>7</td>
<td>29</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Effect of nifedipine and verapamil on epinephrine-potentiated, TXA₂-induced aggregation of gel-filtered human platelets. The platelets were incubated with 200 μM aspirin for 20 min. Then a 15 μl aliquot of nonaggregating dog platelets stirred with 0.33 mM sodium arachidonate was added to the human platelets stirred in an aggregometer. The top curve illustrates the response of human platelets incubated in buffer followed by 0.54 μM epinephrine (E) 1 min before the addition of a TXA₂-containing aliquot of dog platelets (TXA₂). The bottom curve demonstrates that the quantity of TXA₂ transferred was inadequate to cause aggregation of the control platelets. Similarly, the control platelets did not aggregate in response to 0.54 μM epinephrine alone (data not shown). The middle curves illustrate that preincubation of the platelets for 5 min with either 10 μM verapamil or 10 μM nifedipine blocked the aggregation response to epinephrine plus TXA₂.

**ΔT** = change in light transmission.
FIGURE 2. Effect of nifedipine and verapamil on TXA$_2$-induced aggregation of gel-filtered human platelets. The experimental conditions are similar to those in figure 1, except that a 30 μl aliquot of TXA$_2$-containing dog platelets was added to gel-filtered, aspirin-incubated human platelets. The platelets were not preincubated with epinephrine. The top curve illustrates the response of human platelets incubated in buffer to the addition of the aliquot of TXA$_2$-containing dog platelets (TXA$_2$). The curve second from the top illustrates the response of human platelets preincubated with 100 μM verapamil to TXA$_2$. No inhibition was observed with 10 μM verapamil (data not shown). The bottom two curves illustrate the response of human platelets preincubated with 6 or 10 μM nifedipine. Abbreviations as in figure 1.

Human platelet binding of [H]-yohimbine. Specific binding of [H]-yohimbine to intact human platelets was significantly inhibited by 10 μM verapamil but not by 10 μM nifedipine (table 5, figure 5). The number of receptors per platelet was not altered by either drug (table 5).

Discussion

Human platelet aggregation induced by several agonists is inhibited by calcium-channel blockers. Nifedipine and verapamil, plus other calcium-channel blockers, have generally had similar effects on platelet aggregation, but the inhibitory concentrations required in vitro are high (generally > 50 μM), and the effects observed ex vivo after administration to humans have been quite variable. The variability encountered is perhaps not surprising, since these drugs in other tissues have demonstrated significant heterogeneity with regard to binding characteristics and physiologic effects.1, 2, 3

Because calcium-channel blockers have well-documented inhibitory effects on calcium entry into myocardial and smooth muscle cells, it has been postulated that their platelet-inhibitory properties are caused by impaired calcium flux. However, direct evidence to support this mechanism in the platelet is quite limited.7 Human platelets do not appear to have voltage-dependent calcium channels. In addition, no specific human platelet binding of [3H]-nitrendipine or nimodipine (radioligands that bind with high affinity to voltage-dependent calcium channels in cardiac muscle and other tissues) have been demonstrated. However, nitrendipine has been observed to antagonize the rise in free calcium concentration induced by CGP-28392, a dihydropyridine calcium-entry stimulator.39 Other mechanisms by which calcium-channel blockers may inhibit platelet function are an "anesthetic-like" effect on cell membranes.6, 39, 40 inhibition of cyclic AMP phosphodiesterase and/or calmodulin,41, 44, 45 inhibition of fibrinogen binding, inhibition of TXA$_2$ aggregation, and the effect of calcium-channel blockers on ATP release from human platelets.46

FIGURE 3. Experimental conditions as specified in figure 1 except that U46619 was substituted for TXA$_2$ and aspirin incubation was omitted. The top curve illustrates the response of human platelets incubated in buffer followed by 0.054 μM epinephrine (E) 1 min before the addition of 0.06 μM U46619. The bottom curve represents the response of the platelets to 0.06 μM U46619 alone. The middle curves illustrate that preincubation of the platelets for 5 min with either 10 μM verapamil or 2.9 μM nifedipine inhibits the aggregation response to epinephrine plus U46619. Abbreviations as in figure 1.
in nifedipine-induced platelet dysfunction. This mechanism is of potential significance with regard to adverse platelet and blood vessel events in coronary arteries.

It has been postulated that TXA2 formed by platelet activation in atheromatous coronary arteries may induce ischemia by stimulation of intravascular platelet aggregates and/or vasoconstriction. Since TXA2 is a potent vasoconstrictor and platelet-aggregating agent, it is reasonable to hypothesize that these events occur. However, direct confirmatory evidence is lacking. In the case of TXA2-induced vasoconstriction, conflicting evidence exists. Nevertheless, a growing body of experimental and clinical data indicates that platelet activation and fibrin formation occur in coronary artery disease complicated by unstable angina or myocardial infarction. The fact that evidence of platelet/fibrin thrombi is found in the coronary arteries of may patients with unstable angina and in the majority of patients with transmural myocardial infarction or sudden death indicates that platelet activation plays an important role in the pathophysiology of these serious sequelae of atheromatous coronary artery disease. Furthermore, the therapeutic benefits of aspirin (which blocks TXA2 formation) in unstable angina provide additional strong support for this concept. Therefore, inhibition of TXA2-induced

**TABLE 4**

Effect of nifedipine and verapamil on human platelet cyclic AMP in vitro

<table>
<thead>
<tr>
<th></th>
<th>Mean cAMP (pmol/10⁷ platelets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>11.1 ± 4.8</td>
</tr>
<tr>
<td>Nifedipine (10 µM)</td>
<td>8.9 ± 5.2 p &gt; .1⁴⁺</td>
</tr>
<tr>
<td>Verapamil (10 µM)</td>
<td>11.5 ± 3.9 p &gt; .5</td>
</tr>
</tbody>
</table>

⁴⁺Significance of difference between control and drug-incubated platelets (paired t test; n = 15).

**TABLE 5**

Effect of nifedipine and verapamil on specific binding of [³H]-yohimbine to human platelets in vitro

<table>
<thead>
<tr>
<th></th>
<th>[³H]-Yohimbine</th>
<th>[³H]-Yohimbine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sites/platelet</td>
<td>Kᵦ (nM)</td>
</tr>
<tr>
<td>Control (Ethanol)</td>
<td>10 ± 28 ²⁻</td>
<td>2.4 ± 0.6</td>
</tr>
<tr>
<td>Nifedipine (10 µM)</td>
<td>130 ± 34</td>
<td>2.4 ± 0.3 p &gt; .5 ²⁻</td>
</tr>
<tr>
<td>Verapamil (10 µM)</td>
<td>116 ± 37 p &gt; .20</td>
<td>10.5 ± 2.1 p &gt; .001 ²⁻</td>
</tr>
</tbody>
</table>

²⁻Mean ± SD.

²⁻Significance of difference between control and drug-incubated platelets.

**FIGURE 4.** Experimental conditions as specified in figure 3. The top curve illustrates the response of human platelets incubated in buffer to 0.14 µM U46619. The bottom curve demonstrates the inhibitory effect of incubation with 2.9 µM nifedipine for 5 min on U46619-induced platelet aggregation. The middle curve demonstrates the lack of inhibition of U46619-induced platelet aggregation by preincubation for 5 min with 100 µM verapamil. Abbreviations as in figure 1.

A property of some calcium-channel blockers that is known to play a role in inhibition of platelet function is adrenergic receptor antagonism. Verapamil inhibits epinephrine-induced platelet aggregation by binding to α₂-adrenergic receptor sites. However, nifedipine, which also inhibits epinephrine-induced platelet aggregation, has no inhibitory effect on yohimbine binding to α₂-adrenergic receptors. As in previous studies we found that verapamil inhibited yohimbine binding, but nifedipine did not, despite the fact that both drugs in equal concentrations inhibited epinephrine-potentiated, TXA2-induced, or U46619-induced platelet aggregation. Evaluation of the effects of these drugs on platelet aggregation induced by TXA2 alone or by U46619 alone revealed the reason why both drugs had the same functional consequence. Verapamil blocked the contribution of epinephrine to the aggregation response, whereas nifedipine inhibited the platelet response to TXA2 or U46619. Thus two calcium-channel blockers inhibited platelet aggregation induced by the same agonists by different mechanisms.

Although previous studies suggest that inhibition of platelet TXA2 formation may be one mechanism by which calcium-channel blockers inhibit platelet function, we found that an additional mechanism — inhibition of the response to TXA2 — plays an important role.
adverse platelet and blood vessel events may be a beneficial effect of nifedipine therapy.

Inhibition of the platelet response to TXA₂ would be expected to result in an aggregation defect that would functionally resemble that induced by aspirin if it completely blocked the TXA₂ response. The antithrombotic efficacy of nifedipine and verapamil has been directly evaluated in only a limited fashion. In a study of prosthetic vascular grafts in dogs, nifedipine and verapamil significantly reduced platelet deposition on the grafts.64 The degree of inhibition was comparable to that observed with dipyridamole.64 However, the results of several clinical trials suggest that the efficacy of nifedipine as an antithrombotic agent in the coronary circulation is limited because it does not reduce the frequency of myocardial infarction or cardiac death in patients with unstable angina.65-67 Verapamil is similarly ineffective in reducing the occurrence of these events in patients with stable or unstable angina.68 However, both nifedipine and verapamil significantly reduce the severity of angina.65-68 Some of their antian-ginal effects may be due to their platelet inhibitory characteristics.69 Further studies of platelet inhibitory properties of the calcium-channel blockers may help unravel the complexities of the pathogenesis of acute myocardial ischemic events and coronary spasm.

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FIGURE 5. Effect of nifedipine and verapamil on specific equilibrium binding of [³H]-yohimbine to washed, intact human platelets. Specific binding was determined by subtracting nonspecific binding (data not shown), performed in the presence of 10 μM phentolamine, from total binding (data not shown). Platelets were incubated with alcohol in buffer (left), 10 μM nifedipine in alcohol (middle), or 10 μM verapamil in buffer (right), and specific binding of [³H]-yohimbine at the specified concentrations was determined. The saturation binding curves are presented for one representative experiment with each drug and control. The insets present Scatchard plots of the data. The dissociation constants (K_D) and binding sites per platelet (B_max) for these experiments are stated.
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