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Involvement of the Antiplatelet Activity of Magnesium Sulfate in Suppression of Protein Kinase C and the Na^+/H^+ Exchanger

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Key Words
Magnesium sulfate · Platelet aggregation · Protein kinase C · Intracellular Ca^{+2} mobilization · Na^+/H^+ exchanger

Abstract
Magnesium sulfate is widely used to prevent seizures in pregnant women with hypertension. The aim of this study was to examine the inhibitory mechanisms of magnesium sulfate in platelet aggregation in vitro. In this study, magnesium sulfate concentration-dependently (0.6–3.0 m*M*) inhibited platelet aggregation in human platelets stimulated by agonists. Magnesium sulfate (1.5 and 3.0 m*M*) also concentration-dependently inhibited phosphoinositide breakdown and intracellular Ca^{+2} mobilization in human platelets stimulated by thrombin. Rapid phosphorylation of a platelet protein of M_r 47,000 (P47), a marker of protein kinase C activation, was triggered by phorbol-12-13-dibutyrate (PDBu, 50 n*M*). This phosphorylation was markedly inhibited by magnesium sulfate (3.0 m*M*). Magnesium sulfate (1.5 and 3.0 m*M*) further inhibited PDBu-stimulated platelet aggregation in human platelets. The thrombin-evoked increase in pHi was markedly inhibited in the presence of magnesium sulfate (3.0 m*M*). In conclusion, these results indicate that the antiplatelet activity of magnesium sulfate may be involved in the following two pathways: (1) Magnesium sulfate may inhibit the activation of protein kinase C, followed by inhibition of phosphoinositide breakdown and intracellular Ca^{+2} mobilization, thereby leading to inhibition of the phosphorylation of P47. (2) On the other hand, magnesium sulfate inhibits the Na^+/H^+ exchanger, leading to reduced intracellular Ca^{+2} mobilization, and ultimately to inhibition of platelet aggregation and the ATP-release reaction.

Introduction

Clinical findings suggest that magnesium deficiency has a role in various disorders, especially in cardiovascular diseases [1, 24]. Shechter et al. [25, 26] previously demonstrated that intravenous magnesium therapy reduces mortality in patients with acute myocardial infarction who are not eligible for thrombolysis, although mechanisms of the benefit remain unknown. Furthermore, magnesium deficiency and its association with platelet hyperreactivity are well recognized in a variety of diseases including acute myocardial infarction [20], preeclampsia [16], and diabetes mellitus [17]. The increased ability of platelets to aggregate is considered an important risk factor for acute thrombotic events in atherosclerotic coronary arteries.

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Intravascular thrombosis is one of the generators of a wide variety of cardiovascular diseases. Initiation of intraluminal thrombosis is believed to involve platelet adherence and aggregation. Thus, platelet aggregation may play a crucial role in atherothrombotic processes. Indeed, antiplatelet agents (e.g., ticlopidine and aspirin) have been shown to reduce the incidence of stroke in high-risk patients [10]. Magnesium sulfate has been shown to reduce platelet aggregation both in vitro and ex vivo [13, 21]. Furthermore, in vitro studies have shown reduced release by platelets of β-thromboglobulin and thromboxane B_2 with increasing magnesium concentrations (0.5–8.0 m*M*) [10, 11]. Shechter et al. [27] reported that oral magnesium therapy can significantly improve the condition of patients with coronary artery diseases. Apart from the direct antiplatelet effect, an antithrombotic effect can also be derived from nitric oxide and prostacyclin, as magnesium has been shown to stimulate the release of these vasodilating and antiaggregatory substances from the endothelium [17, 36].

On the other hand, findings from studies of the mechanisms of magnesium in antiplatelet aggregation have relatively rarely been compared with results from other antiplatelet drugs (such as aspirin and ticlopidine). It was previously shown that magnesium inhibits platelet aggregation in vitro [13, 21, 36]. We also reported that magnesium sulfate may initially induce membrane fluidity changes with resulting interference of fibrinogen binding to the glycoprotein IIb/IIIa complex and that it triggers the formation of cyclic AMP, thereby leading to inhibition of platelet aggregation [28]. However, the detailed mechanisms underlying the signaling pathways in platelets still remain obscure. We therefore further examined the influence of magnesium sulfate on washed human platelets, and utilized the findings to characterize the detailed mechanisms involved in this influence.

Materials and Methods

Materials

Sodium citrate, luciferin-luciferase, indomethacin, phorbol-12-13-dibutyrate (PDBu), magnesium sulfate, nigericin, Dowex-1 (100–200 mesh; X_8, chloride form), myoinositol, prostaglandin E_1 (PGE_1), arachidonic acid, apyrase, heparin, ADP, and thrombin were purchased from Sigma Chemical Co. (St. Louis, Mo., USA). Fura 2-AM and BCECF-AM were purchased from Molecular Probe (Eugene, Oreg., USA). Myo-2-[^{3}H] inositol was purchased from Amersham (Buckinghamshire, UK). KT-5720 was purchased from Calbiochem (San Diego, Calif., USA).

Preparation of Human Platelet Suspensions

Human platelet suspensions were prepared as previously described [29]. In this study, human volunteers gave informed consent. In brief, blood was collected from healthy human volunteers who had taken no medicine during the preceding 2 weeks, and was mixed with acid/citrate/glucose (9:1, v/v). After centrifugation at 120 *g* for 10 min at room temperature, the supernatant (platelet-rich plasma) was supplemented with PGE_1 (0.5 μ*M*) and heparin (6.4 IU/ml), then incubated for 10 min at 30°C and centrifuged at 500 *g* for 10 min. PGE_1 increases cyclic AMP formation to prevent platelet aggregation in preparations of platelet suspensions. Washed platelets were finally suspended in Tyrode's solution containing bovine serum albumin (3.5 mg/ml) and adjusted to a concentration of 4.5×10^8 platelets/ml. The final concentration of Ca^{+2} in Tyrode's solution was 1 m*M*.

Platelet Aggregation

The turbidimetric method was applied to measure platelet aggregation [5], using a Lumi-Aggregometer (Payton, Scarborough, Canada). Platelet suspensions (4.5×10^8 platelets/ml, 0.4 ml) were prewarmed to 37°C for 2 min (stirring at 1,200 rpm) in a silicone-treated glass cuvette. Magnesium sulfate or magnesium chloride (0.6–3.0 m*M*) was added 3 min before the addition of platelet-aggregation inducers. The reaction was allowed to proceed for at least 6 min, and the extent of aggregation was expressed in light-transmission units.

Labeling of Membrane Phospholipids and Measurement of the Production of [^{3}H]-Inositol Phosphates

This was carried out as previously described [12]. Briefly, citrated human platelet-rich plasma was centrifuged, and the pellets were suspended in Tyrode's solution containing [^{3}H]-inositol (75 μCi/ml). Platelets were incubated for 2 h followed by centrifugation, and were finally resuspended in Ca^{+2}-free Tyrode's solution (5×10^8/ml). Magnesium sulfate (1.5 and 3.0 m*M*) was preincubated with 1 ml of loaded platelets at room temperature for 3 min, and thrombin (0.02 U/ml) was then added to trigger aggregation. The reaction was stopped after 6 min, and samples were centrifuged at 1,000 *g* for 4 min. The inositol phosphates of the supernatants were separated in a Dowex-1 anion exchange column. Only [^{3}H]-inositol monophosphate (IP) was measured as an index of total inositol phosphate formation.

Measurement of Platelet [Ca^{+2}]i Mobilization by Fura 2-AM Fluorescence

Citrated whole blood was centrifuged at 120 *g* for 10 min. The supernatant was protected from light and incubated with Fura 2-AM (5 μ*M*) at 37°C for 1 h. Human platelets were then prepared as described above. Finally, the external Ca^{+2} concentration of the platelet suspensions was adjusted to 1 m*M*. The [Ca^{+2}]i rise was measured using a fluorescence spectrophotometer (CAF 110, Jasco, Tokyo, Japan) at excitation wavelengths of 340 and 380 nm, and an emission wavelength of 500 nm. [Ca^{+2}]i was calculated from the fluorescence, using 224 n*M* as the Ca^{+2}-Fura 2 dissociation constant [9].

Measurement of Protein Kinase C Activity

Washed human platelets (2×10^9/ml) were incubated for 60 min at 37°C with phosphorus-32 (0.5 mCi/ml). Platelet suspensions were next washed twice with Tris-saline buffer. The [^{32}P]-labeled platelets were preincubated with magnesium sulfate (3.0 m*M*) in an aggre-

gometer for 3 min, PDBu (50 n*M*) was then added for 1 min to trigger protein kinase C activation. Activation was terminated by the addition of Laemmli sample buffer, and analyzed by electrophoresis (12.5%, w/v) as described previously [8]. The gels were dried, and the relative intensities of the radioactive bands were analyzed using a Bio-imaging analyzer system (FAL2000, Fuji, Tokyo, Japan), and were expressed as photostimulated luminescence per square millimeter (PSL/mm^2).

Platelet pHi Measurement

Platelet pHi was measured using the fluorescent probe, BCECF-AM, according to a previously described method [34]. Washed platelets were incubated with 5 μ*M* BCECF-AM at 37 °C for 30 min in a Hepes-buffered solution (145 m*M* NaCl, 5 m*M* KCl, 1 m*M* $MgSO_4$, 1 m*M* $CaCl_2$, 10 m*M* Hepes and 5 m*M* glucose, pH 7.4) and then centrifuged at 450 *g* for 8 min. Washed pellets were finally suspended in buffer and adjusted to $4.5.10^8$/ml. Leukocyte contamination was less than 0.01%. Aliquots of this platelet suspension (50 μl) were transferred to a cuvette containing 2 ml Hepes-buffered solution in a dual-excitation wavelength spectrofluorometer (CAF 110, Jasco). Fluorescence signals for BCECF-AM were recorded at 430- and 490-nm excitation wavelengths with an emission wavelength of 530 nm (5-nm slit). The background fluorescence of platelets was subtracted from each reading. Calibration was carried out after diluting the BCECF-loaded platelets in high-K^+ buffer (120 m*M* KCl, 30 m*M* NaCl, 1 m*M* $MgSO_4$, and 5 m*M* glucose) in the presence of nigericin (0.2 mg/ml), as described by Horne et al. [11]. In all experiments, platelets were stimulated by thrombin (0.02 U/ml) to trigger the Na^+/H^+ exchanger.

Statistical Analysis

The experimental results are expressed as the mean ± SEM and are accompanied by the number of observations. Data were assessed using analysis of variance (ANOVA). If this analysis indicated significant differences among the group means, then each group was compared using the Newman-Keuls method. A p value of <0.05 was considered statistically significant.

Results

Effect of Magnesium Sulfate on Platelet Aggregation in Human Platelet Suspensions

Magnesium sulfate (0.6–3.0 m*M*) concentration-dependently inhibited platelet aggregation stimulated by thrombin (0.02 U/ml) in human platelets (fig. 1A). It also similarly inhibited ADP (20 μ*M*)-induced platelet aggregation in the presence of fibrinogen (300 μg/ml) (fig. 1B). Furthermore, magnesium sulfate inhibited the ATP-release reaction when stimulated by agonists (i.e., thrombin, fig. 1A). The IC_{50} values of magnesium sulfate for platelet aggregation induced by thrombin and ADP were estimated to be approximately 2.6 and 1.7 m*M*, respectively. Furthermore, magnesium chloride (1.5 and 3.0 m*M*) also showed a similar concentration-dependent inhibitory effect on agonist-induced platelet aggregation (fig. 1C). Both salts were used for platelet aggregation stimulated by all agonists, and no significant differences were found as seen in figure 1. These results indicate that the antiplatelet activity of magnesium sulfate is specific for magnesium ion. Furthermore, platelets were preincubated with a higher concentration of magnesium sulfate (5.0 m*M*) or normal saline for 30 min, followed by 2 washes with Tyrode's solution, we found that there were no significant differences between the aggregation curves of either platelet preparations stimulated by thrombin (0.02 U/ml), indicating that the effect of magnesium sulfate on inhibition of platelet aggregation occurs in a reversible manner (data not shown). In the following experiments, we used thrombin as an agonist to explore the inhibitory mechanisms of magnesium sulfate in platelet aggregation.

Effect of Magnesium Sulfate on Phosphoinositide Breakdown in Human Platelet Suspensions

Phosphoinositide breakdown occurs in platelets activated by many different agonists [6]. In this study, we found that thrombin (0.02 U/ml) induced the rapid formation of radioactive IP, IP_2, and IP_3 in human platelets loaded with [^{3}H]-inositol. We only measured [^{3}H]-IP formation as an index of total inositol phosphate formation. In this study, thrombin (0.02 U/ml) resulted in about a 2.3-fold rise in IP formation compared to that in resting platelets [$(4.6 \pm 1.6$ vs. $10.4 \pm 1.6) \times 10^3$ cpm, $n = 6$, $p < 0.05$; data not shown]. In the presence of magnesium sulfate (1.5 and 3.0 m*M*), the radioactivity of IP formation in thrombin-stimulated human platelets markedly decreased [1.5 m*M*, $(6.1 \pm 0.5) \times 10^3$ cpm, $n = 6$, $p < 0.05$; 3.0 m*M*, $(6.0 \pm 0.4) \times 10^3$ cpm, $n = 6$, $p < 0.05$; data not shown]. These results indicate that magnesium sulfate interferes with phosphoinositide breakdown in human platelets stimulated by thrombin.

Effect of Magnesium Sulfate on $[Ca^{+2}]i$ Mobilization

Free cytoplasmic Ca^{+2} concentrations in human platelets were measured by the Fura 2-AM loading method. As shown in figure 2, thrombin (0.02 U/ml) evoked an increase in $[Ca^{+2}]i$ from 45.8 ± 6.2 to 316.5 ± 29.4 n*M*. This thrombin-evoked increase in $[Ca^{+2}]i$ was markedly inhibited in the presence of magnesium sulfate (1.5 m*M*, $77.8 \pm 6.2\%$; 3.0 m*M*, $92.7 \pm 8.9\%$; $n = 4$). This suggests that magnesium sulfate exerts an inhibitory effect on $[Ca^{+2}]i$ mobilization in human platelets stimulated by thrombin.

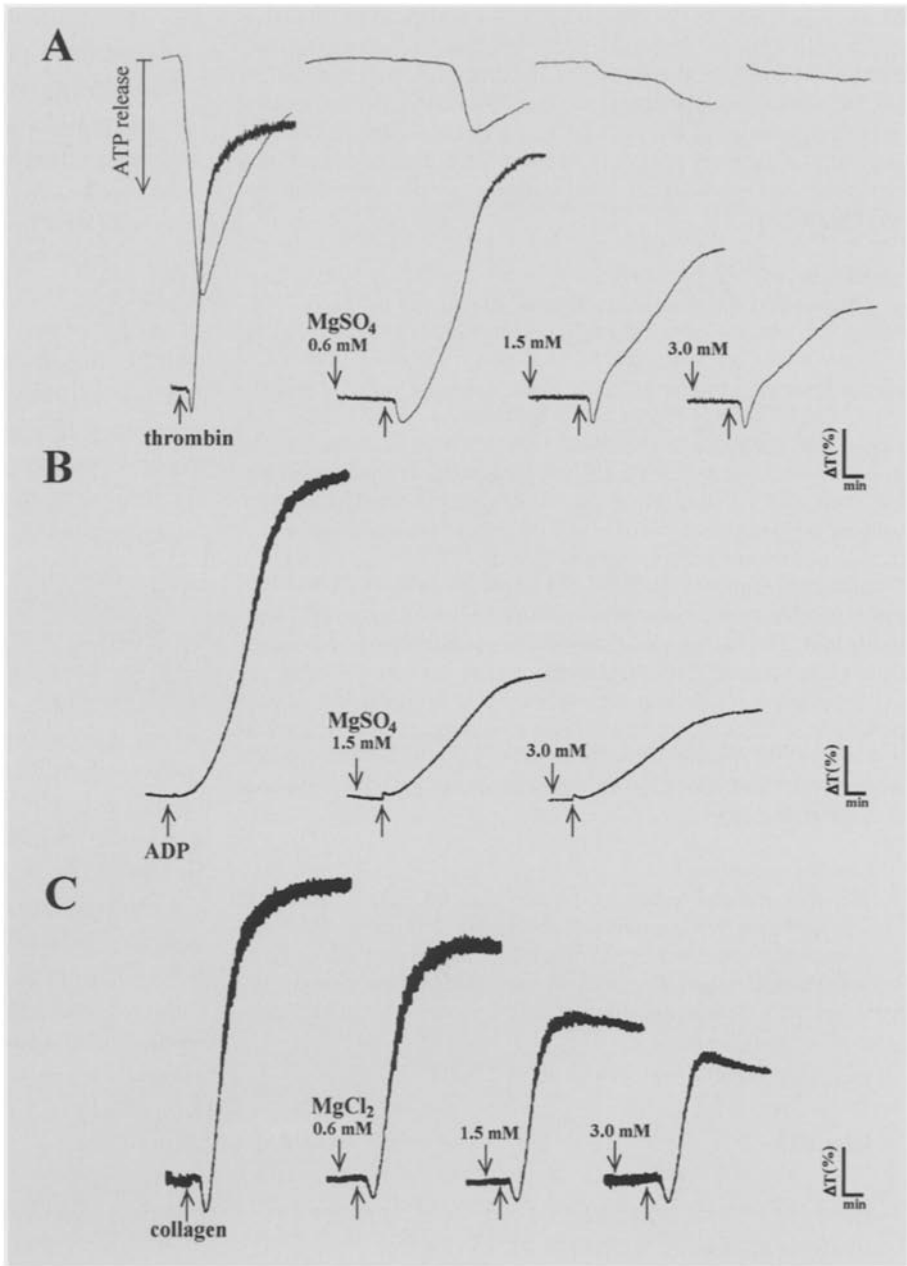

Fig. 1. Tracing curves of magnesium sulfate on thrombin (0.02 U/ml)-induced (**A**) as well as ADP (20 μ*M*)-induced platelet aggregation (**B**), and the curve of magnesium chloride on collagen (1 μg/ml)-induced platelet aggregation in washed human platelet suspensions (**C**). Platelets were preincubated with magnesium sulfate (0.6–3.0 m*M*) or magnesium chloride (0.6–3.0 m*M*) for 3 min; agonists were then added to trigger platelet aggregation and ATP release (upper tracings, **A**). Curves are representative examples of six similar experiments.

Effect of Magnesium Sulfate on PDBu-Stimulated Phosphorylation of the 47-kD Protein

Stimulation of platelets with a number of different agonists, and PDBu, in particular, induces activation of protein kinase C, which then phosphorylates proteins of M_r 40,000–47,000 in addition to other proteins [32]. In this study, phosphorylation was performed to examine the role of magnesium sulfate in activating protein kinase C in human platelets. When PDBu (50 n*M*) was added to human platelets prelabeled with $^{32}PO_4$ for 2 min, a protein with an apparent M_r of 47,000 (P47) was predominately phosphorylated as compared with resting platelets (fig. 3). On the other hand, magnesium sulfate (3.0 m*M*) markedly inhibited the phosphorylation of P47 in human platelets stimulated by PDBu (50 n*M*) (fig. 3). In this study, the extent of radioactivity in P47 was expressed as the relative detection density (PSL/mm^2) of the radioactive bands. On the other hand, magnesium sulfate (1.5 and 3.0 m*M*) also concentration-dependently inhibited PDBu (50 n*M*)-induced platelet aggregation in human

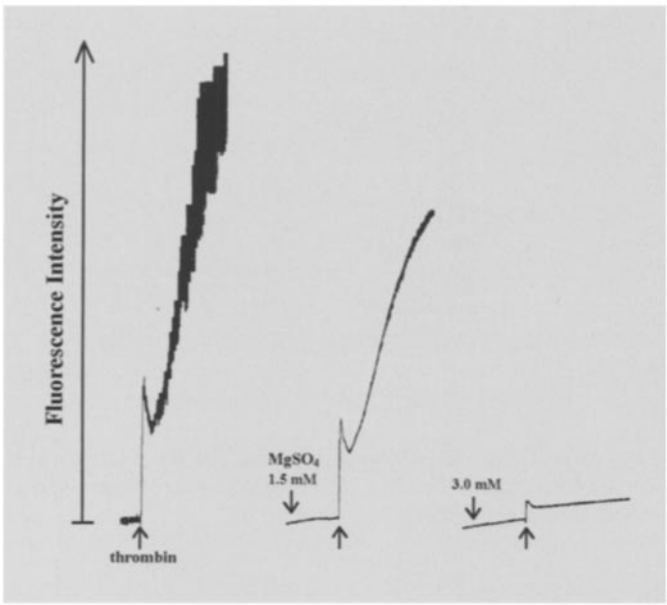

Fig. 2. Effect of magnesium sulfate on thrombin-induced intracellular Ca^{+2} mobilization in Fura 2-AM-loaded human platelets. Platelet suspensions were preincubated with Fura 2-AM (5 μM), followed by the addition of thrombin (0.02 U/ml) in the absence or presence of magnesium sulfate (1.5 and 3.0 mM), which was added 3 min prior to the addition of thrombin. Profiles are representative examples of four similar experiments.

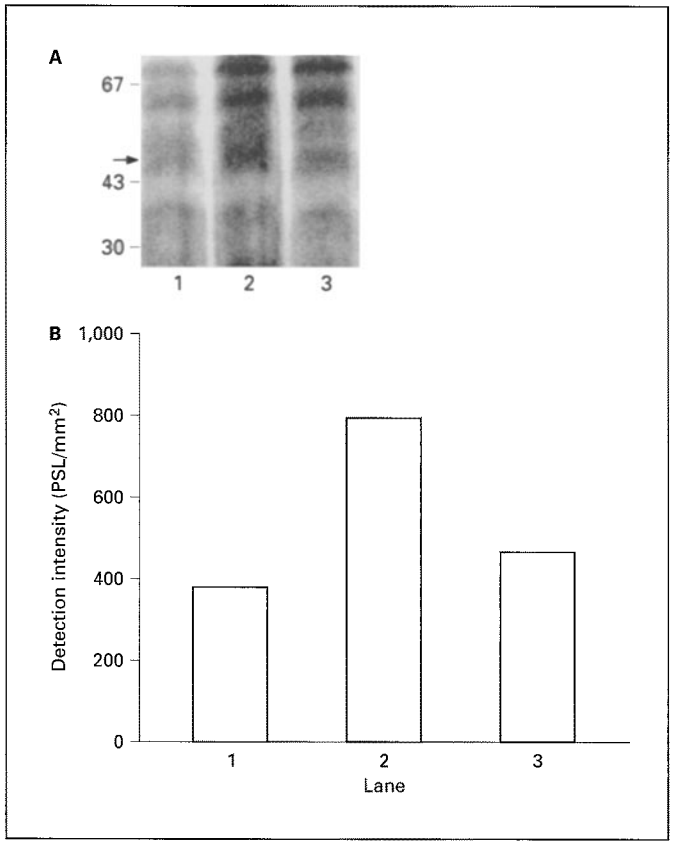

Fig. 3. A Effect of magnesium sulfate on phosphorylation of a protein of M_r 47,000 (P47) in human platelets challenged with PDBu. Platelets were preincubated with magnesium sulfate (3.0 mM) before challenge with PDBu (50 nM). Lane 1 = Platelets with Tyrode's solution; lane 2 = platelets with PDBu (50 nM); lane 3 = platelets with magnesium sulfate (3.0 mM) for 3 min followed by the addition of PDBu (50 nM). The arrow indicates a protein of M_r 47,000 (P47). **B** The relative detection densities of the radioactive bands are expressed as PSL/mm^2. Data are representative examples of four similar experiments.

platelets (fig. 4). These results indicate that magnesium sulfate can directly interfere with the activation of protein kinase C in human platelets.

Effect of Magnesium Sulfate on Thrombin-Evoked pHi Changes in Platelets

Figure 5 shows pHi changes triggered by thrombin (0.02 U/ml) in BCECF-AM-loaded platelets. The resting platelet pHi value was about 7.15 ± 0.03 (n = 5) in washed human platelets. The addition of thrombin (0.02 U/ml) resulted in an increase in BCECF fluorescence equivalent to an increase in pHi values of about 0.042 ± 0.012 (fig. 5). This thrombin-evoked increase in pHi values was markedly inhibited in the presence of magnesium sulfate (3.0 mM, 0.009 ± 0.0005) (fig. 5). Furthermore, both PDBu (50 nM) and KT-5720 (3 μM), an inhibitor of cyclic AMP-dependent protein kinase [30], significantly reversed the inhibitory effect of magnesium sulfate (3.0 mM))in thrombin-evoked increase in pHi value (fig. 6). In addition, cariporide (0.5 μM), a Na^+/H^+ exchange inhibitor [3], significantly inhibited the thrombin-evoked pHi increase by about 90% in this study (0.005 ± 0.001, n = 3, $p < 0.001$, data not shown).

Discussion

Magnesium sulfate is the agent most commonly used for treatment of eclampsia and for prophylaxis against eclampsia in patients with severe preeclampsia [16]. The principal objective of this study was to describe the detailed mechanisms involved in the inhibition of agonist-induced human platelet aggregation by magnesium sulfate. This inhibitory effect of magnesium sulfate was demonstrable with the use of various agonists, such as thrombin and ADP. Inhibition was directly proportional to the pharmacological concentrations of magnesium sulfate used. Lucas et al. [16] suggested that the magnesium sulfate regimen for preeclampsia should consist of an ini-

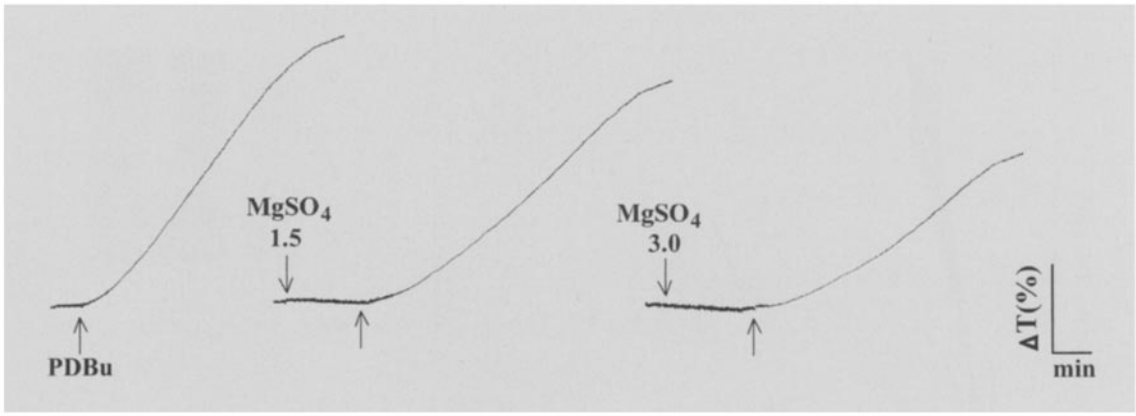

Fig. 4. Effect of magnesium sulfate on PDBu-induced platelet aggregation in washed human platelets. Platelets were preincubated with magnesium sulfate (1.5 and 3.0 m*M*) for 3 min, PDBu (50 n*M*) was then added to trigger platelet aggregation. Curves are representative examples of four similar experiments.

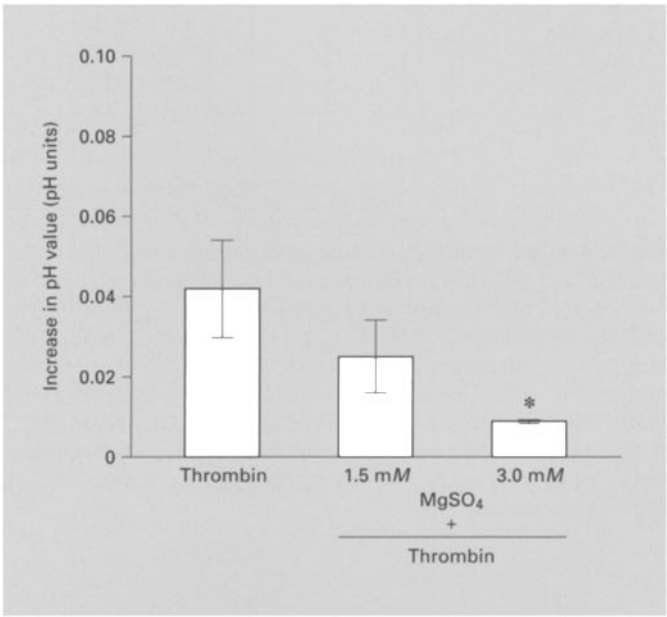

Fig. 5. Effect of magnesium sulfate on the thrombin-triggered increase in intracellular pH in BCECF-AM-loaded platelets. Platelet suspensions (4.5×10^8/ml) were preincubated with BCECF-AM (5 μ*M*) at 37°C for 30 min, followed by the addition of thrombin (0.02 U/ml) to trigger intracellular alkalinization in the presence or absence of magnesium sulfate (1.5 and 3.0 m*M*). Data are presented as the means ± SEM (n = 5). * $p < 0.001$ as compared with the thrombin-treated group without magnesium sulfate.

tial loading dose of 4 g of magnesium sulfate (i.v.) followed by a 10-gram intramuscular dose and a maintenance dose of 5 g given intramuscularly every 4 h. In general, the therapeutic concentration is considered to be between 2 and 4 m*M* [19, 31]. However, this is based on clinical experience and not directly related to the suppression of eclamptic convulsions. In this study, magnesium sulfate was employed at concentrations of about 0.6–3.0 m*M*, which inhibited platelet aggregation induced by agonists. This result indicates that the pharmacological concentrations of magnesium sulfate employed to inhibit platelet aggregation in vitro are reasonably close to those of blood concentrations obtained during a magnesium sulfate regimen in vivo. In this study, platelet aggregation induced by these agonists (i.e., thrombin) appeared to be affected in the presence of magnesium sulfate. Therefore, this partly infers that magnesium sulfate may affect intracellular Ca^{+2} mobilization (fig. 2), and this is in accord with the concept that intracellular Ca^{+2} release is responsible for platelet aggregation. Additionally, Mg^{+2} influences the regulation of cytosolic free Ca^{+2} concentrations, the most important intracellular second messenger, by inhibiting the influx of Ca^{+2} into cytoplasma via Ca^{+2} channels and by facilitating the uptake of Ca^{+2}-ATPase-driven Ca^{+2} into different intracellular stores in cardiac myocytes [23]. Therefore, magnesium has been likened to a naturally occurring Ca^{+2} channel blocker [23].

Stimulation of platelets by agonists (i.e., thrombin) results in phospholipase C-catalyzed hydrolysis of the minor plasma membrane phospholipid, phosphatidylinositol 4,5-bisphosphate, with concomitant formation of inositol 1,4,5-trisphosphate and diacylglycerol [6]. There

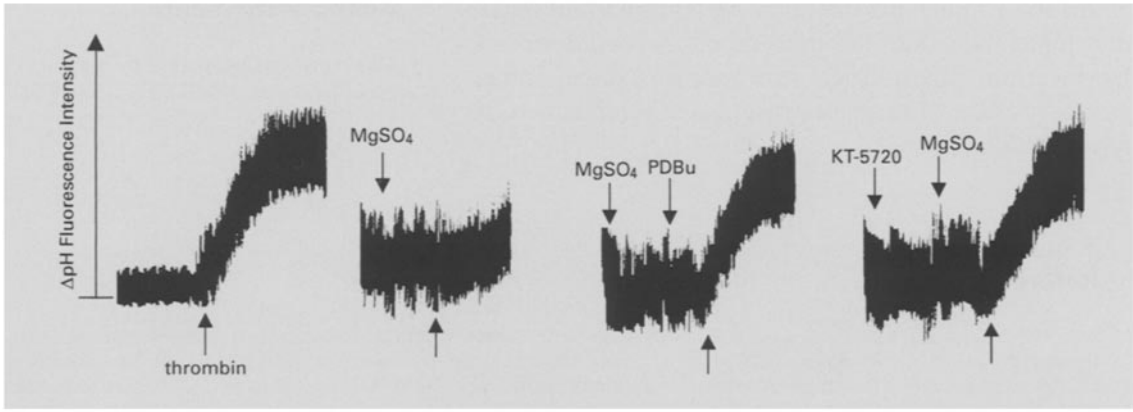

Fig. 6. Effects of PDBu and KT-5720 in the magnesium sulfate-mediated inhibitory effect on the thrombin-triggered increase in intracellular pH in BCECF-AM-loaded platelets. Platelet suspensions (4.5×10^8/ml) were preincubated with magnesium sulfate (3.0 m*M*) in the absence or presence of PDBu (50 n*M*) or KT-5720 (3 μ*M*), followed by the addition of thrombin (0.02 U/ml) to trigger intracellular alkalinization in BCECF-AM-loaded platelets. Profiles are representative examples of three similar experiments.

is strong evidence that inositol 1,4,5-trisphosphate induces the release of Ca^{+2} from intracellular stores [4]. Diacylglycerol activates protein kinase C, inducing protein phosphorylation and a release reaction. In this study, phosphoinositide breakdown of thrombin-activated platelets was inhibited by magnesium sulfate, suggesting that the antiplatelet activity of magnesium sulfate affects signal transduction related to the inhibition of phosphoinositide breakdown. Furthermore, activation of protein kinase C in human platelets occurred in response to PDBu, which is known to intercalate membrane phospholipid and form a complex with protein kinase C translocated to the membrane [15]. The most important finding in this study is that magnesium sulfate may interfere with the activation of protein kinase C in human platelets.

On the other hand, activation of platelets by a variety of agonists (i.e., thrombin and ADP) is associated with stimulation of the Na^+/H^+ exchanger [14, 33]. This mode of activation of the Na^+/H^+ exchanger usually induces a rise in cytosolic Ca^{+2}, granule secretion, stimulation of a shape change, and aggregation [14]. Basal pHi is normally maintained within a narrow range, and even small changes in pHi may have significant effects on platelet activity. In many cell types, including fibroblasts, hepatocytes, and smooth muscle cells, Na^+/H^+ exchange activity is regulated by $[Ca^{+2}]i$ and protein kinase C (fig. 6) [14, 18]. Furthermore, Kimura et al. [14] reported that cyclic nucleotides (i.e., cyclic AMP) modulate Na^+/H^+ exchange in human platelets. Inhibition of Na^+/H^+ exchange by cyclic AMP has also been demonstrated in other cells, such as epithelia of the urinary system and in osteoblast-like cells [7, 22]. Thus, an agent (i.e., parathyroid hormone or dopamine) known to stimulate adenylate cyclase in these cells can also inhibit the Na^+/H^+ exchanger [7, 22]. In addition, magnesium sulfate (1.5 and 3.0 m*M*) increased the formation of cyclic AMP in human platelets as described previously [28]. The importance of cyclic AMP in modulating platelet reactivity is well established. In addition to inhibiting most platelet responses, elevated levels of cyclic AMP negatively affected the action of protein kinase C [35]. Therefore, relationships among phosphoinositide breakdown, $[Ca^{+2}]i$, cyclic nucleotides, and the Na^+/H^+ exchanger may play important roles in mediating the antiplatelet activity of magnesium sulfate.

In conclusion, the observations of this study suggest that magnesium sulfate inhibits agonist-induced human platelet aggregation. This inhibitory effect may involve the following mechanisms: (1) Magnesium sulfate may inhibit the activation of protein kinase C and phosphoinositide breakdown, followed by inhibition of the Na^+/H^+ exchanger and/or intracellular Ca^{+2} mobilization and phosphorylation of P47. (2) Magnesium sulfate triggers the formation of cyclic AMP which subsequently inhibits the Na^+/H^+ exchanger and protein kinase C activation. This leads to a reduction in intracellular alkalinization and intracellular Ca^{+2} mobilization, and ultimately inhibition of platelet aggregation. Platelet aggregation plays a role in a variety of thromboembolic disorders, including myocardial infarction, atherosclerosis, and stroke. Results

of this study imply that treatment with magnesium sulfate may lower the risk of thromboembolic-related disorders. However, the physiological relevance of a direct antiaggregatory effect of magnesium sulfate still remains to be further studied.

Acknowledgments

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