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Propofol Has Both Enhancing and Suppressing Effects on Human Platelet Aggregation In Vitro

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Background: **Volatile anesthetics are known to suppress platelet aggregation. In contrast, there is conflicting information regarding the effect of propofol on platelet function. The present study was designed to clarify the effects of propofol on platelet function and the mechanisms underlying these effects.**

Methods: **Propofol or an equivalent volume of 10% Intralipos (as a control) was added to test tubes 5 min before the induction of each reaction. Platelet aggregation induced by epinephrine, arachidonic acid (AA), prostaglandin G_2 (PGG_2), or STA_2 (a thromboxane A_2 [TXA_2] analog) was measured using an eight-channel aggregometer. To determine type 1 cyclooxygenase activity, AA (0.5 mM) was added to an assay mixture containing type 1 cyclooxygenase, and the concentration of the final product, malonaldehyde, was measured by spectrophotometry. Epinephrine-, adenosine diphosphate-, AA-, and PGG_2-induced TXA_2 formation was measured using a commercially available radioimmunoassay kit. To estimate TXA_2 receptor-binding affinity, ^{3}H-S145, a specific TXA_2 receptor antagonist, was added, and the radioactivity of receptor-bound ^{3}H-S145 was determined using a liquid scintillation analyzer. Inositol 1,4,5-triphosphate formation was measured in STA_2-stimulated platelets using a commercially available inositol 1,4,5-triphosphate assay kit.**

Results: **Propofol (40 μM) enhanced, whereas 100 μM suppressed, adenosine diphosphate– and epinephrine-induced secondary aggregation without affecting primary aggregation. Propofol (40 μM) also enhanced, but 100 μM suppressed, AA-induced aggregation. Propofol (100 μM) enhanced PGG_2- and STA_2-induced aggregation. Propofol (100 μM) suppressed AA-induced TXA_2 formation but did not alter that induced by PGG_2. Propofol (30–100 μM) suppressed AA- induced malonaldehyde formation, indicating inhibition of type 1 cyclooxygenase activity. Propofol did not alter TXA_2 receptor-binding affinity. Propofol (30 and 100 μM) augmented inositol 1,4,5-triphosphate formation in STA_2-stimulated platelets.**

Conclusions: **The present findings clearly indicate that high concentrations of propofol suppress the activity of type 1 cyclooxygenase, the enzyme that converts AA to PGG_2. Furthermore, propofol also enhanced STA_2-induced inositol 1,4,5-triphosphate formation. These results may explain the inconsistent findings of previous investigators. (Key words: Eicosanoids; G-protein; intravenous anesthetics; phospholipase; receptor.)**

ALTHOUGH platelet function directly affects hemostasis, our knowledge regarding the effects of anesthetics on platelet function is still limited. Suppression of platelet function by halothane and sevoflurane has been demonstrated by *in vivo*[1,2] and *in vitro*[3–8] studies. We[9,10] have previously shown that the suppressive effect of halothane on platelet aggregation is caused by the suppression of both type 1 cyclooxygenase (COX1) activity and thromboxane A_2 (TXA_2) receptor-binding affinity, whereas that of sevoflurane is caused by COX1 inhibition. Other investigators[7] have postulated that the effect of halothane on thrombin-induced platelet aggregation may be mediated by decreased inositol 1,4,5-triphosphate (IP_3) or increased cyclic adenosine monophosphate levels. In contrast to volatile anesthetics, however, published information regarding the effect of propofol on platelet aggregation is inconsistent. *In vitro* studies by Cruz *et al.*[11] and Aoki *et al.*[12] showed that platelet

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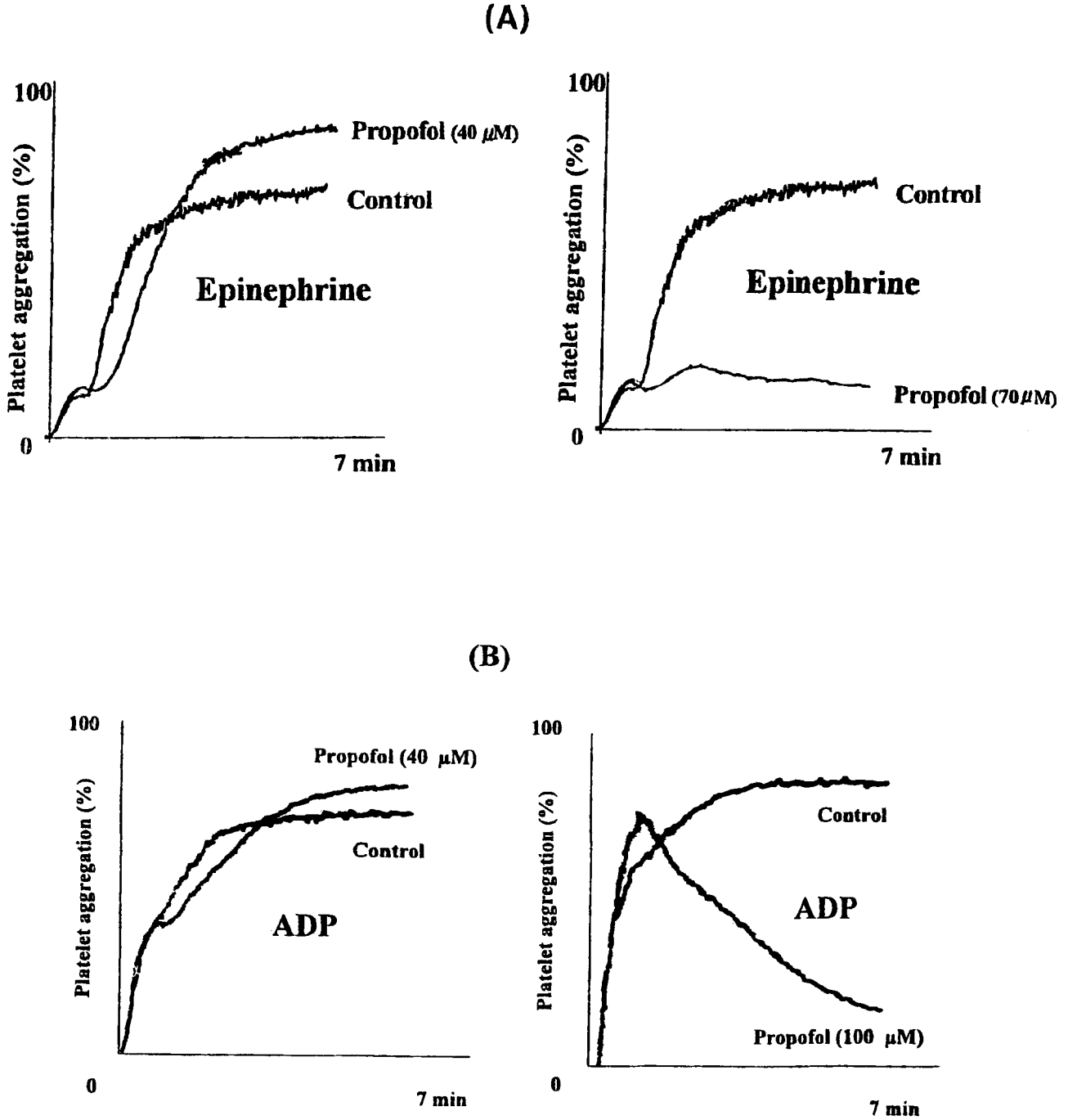

Fig. 1. Typical recordings of platelet aggregation, induced by (*A*) 2 μM epinephrine, (*B*) 1 μM adenosine diphosphate, (*C*) 1 mM arachidonic acid, (*D*) 25 μM prostaglandin G_2, and (*E*) 1 μM STA_2 (a thromboxane A_2 analog) in the presence of propofol (in concentrations indicated in the figure) or equivalent volume of Intralipos.

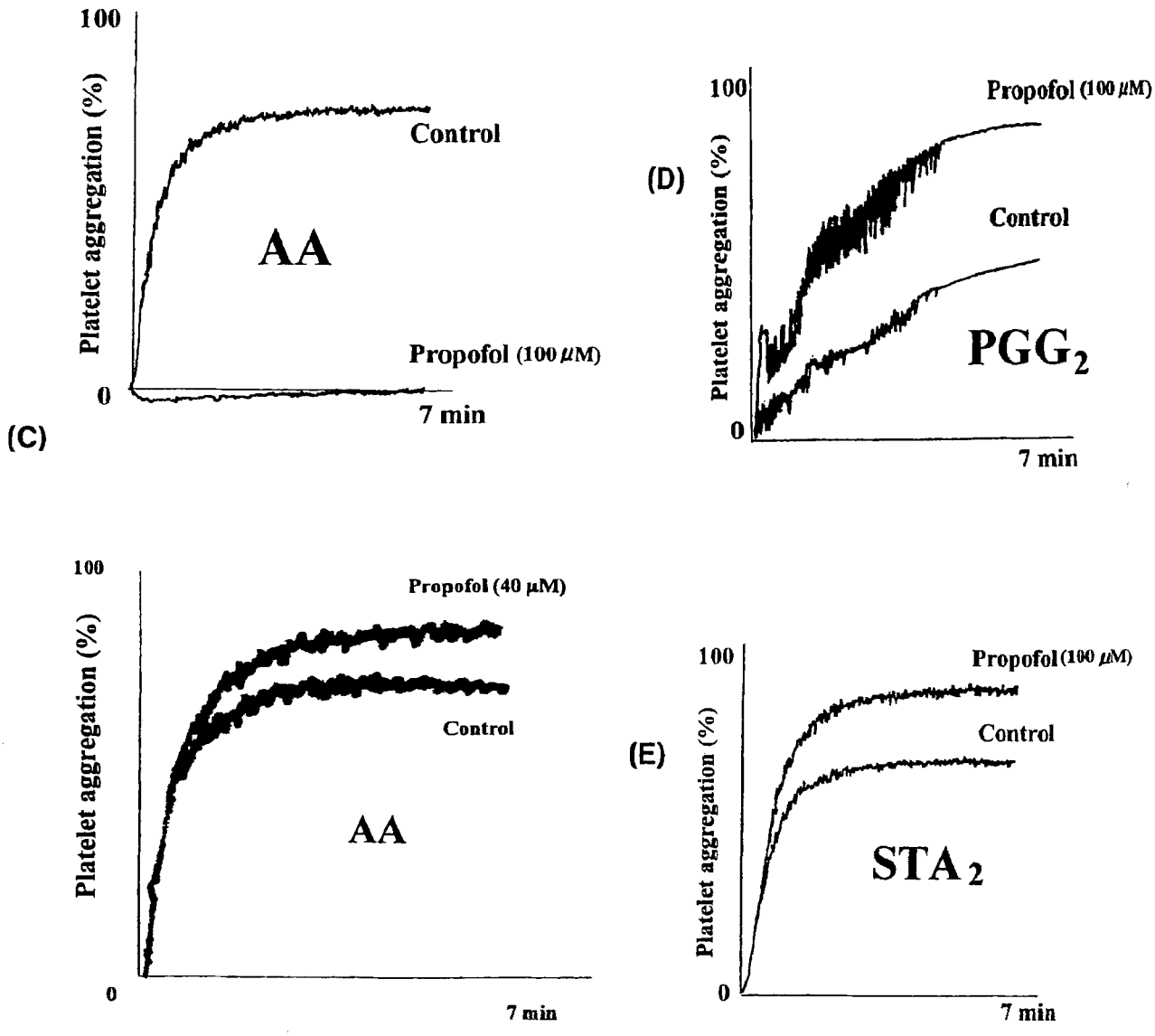

Fig. 1. (*continued*)

aggregation was suppressed by propofol, but an *in vivo* study by Turkan *et al.*,[13] no alteration in platelet function was observed during anesthesia with propofol. The present study was undertaken to elucidate the effects of propofol on platelet function and the underlying mechanism to explain this inconsistency. Platelet aggregation, TXA_2 formation, IP_3 formation, and TXA_2 receptor-binding affinity were studied.

Materials and Methods

The study was conducted in accordance with the human research standards of the institutional ethics committee. Venous blood was obtained from 10 healthy volunteers (4 women and 6 men) aged 27 to 43 yr old (mean age, 34.9 ± 4.79) who had taken no drugs known to affect platelet aggregation for at least 2 weeks. The blood was placed in tubes containing a 10% volume of 3.8% weight/volume trisodium citrate and was centrifuged at 160*g* for 10 min to prepare platelet-rich plasma (PRP) or at 1,600*g* for 30 min to prepare platelet-poor plasma (PPP). The platelet count of the PRP was adjusted to 300,000/μl by adding PPP. PRP and PPP were then stored at room temperature. PRP was used for the aggregation studies and TXA_2 radioimmunoassay. To pre-

pare washed platelets for the binding assay and IP_3 measurement, a 10% volume of 100 mM EDTA (*p*H 7.4) was added to PRP, and the mixture was centrifuged at 900*g* for 15 min. The platelet pellet was suspended in buffer A, which was composed of 8 mM Na_2HPO_4, 2 mM NaH_2PO_4, 10 mM EDTA, 5 mM KCl, and 135 mM NaCl (*p*H 7.2), then recentrifuged at 900*g* for 15 min. Platelet pellets for the binding assay were finally suspended in buffer B, which was composed of 25 mM Tris-HCl, 1 mM EGTA, 5 mM $MgCl_2$, and 138 mM NaCl (*p*H 7.5), and the platelet counts were adjusted to 1,000,000/μl by adding buffer B. Platelet pellets for IP_3 measurement were finally suspended in HEPES buffer, which was composed of 10 mM HEPES, 145 mM NaCl, 5 mM KCl, 0.5 mM Na_2HPO_4, and 6 mM glucose (*p*H 7.5), and the platelet counts were adjusted to 1,000,000/μl by adding HEPES buffer. The washed platelets were stored in Ca^{2+}-free buffer at 0°C for 1 h. A few minutes before being used, the Ca^{2+} concentration of the washed platelets suspended in HEPES buffer was adjusted to 1 mM by adding $CaCl_2$.

Aggregation Study

Propofol and 10% Intralipos (Yoshitomi Pharmaceutical Industries, Osaka, Japan) were appropriately diluted previously by distilled water to adjust adding volume to 1–2 μl. An aliquot of propofol (10–100 μM) or an equivalent volume of 10% Intralipos was added directly to PRP using a micropipet (0.4–2 μl) and incubated at 37°C for a few minutes. The ingredient of Intralipos is essentially the same as the solvent of propofol or Intralipid (commercially available from several companies, including Ohtsuka Pharmacological Company, Tokyo, Japan). Five minutes before analysis, 200-μl aliquots of PRP containing propofol or Intralipos were placed into siliconized glass tubes that were kept at 37°C and stirred continuously before and during the experiments. Platelet aggregation induced by adding (+)-9,11-epithia-11, 12-methano-TXA_2 (STA_2; 0.5–1 μM), arachidonic acid (AA; 0.5–1 mM), prostaglandin G_2 (PGG_2, 25 μM), adenosine diphosphate (ADP; 1–5 μM), or epinephrine (0.5–10 μM) was measured at 37°C by recording the increase in light transmission using an eight-channel aggregometer (MCM Hematracer VI; MC Medical Inc., Tokyo, Japan) (n = 5 each). The light transmission of PPP containing Intralipos, in volume equivalent to that of propofol to be tested, was taken as 100%. Percent aggregation at 7 min after stimulation was analyzed statistically in the presence of propofol or equivolume of Intralipos by unpaired *t* test.

Radioimmunoassay of TXB_2

Platelet aggregation was induced by ADP (1 μM), epinephrine (2 μM), AA (1 mM), and PGG_2 (25 μM) in the presence of propofol (40 or 100 μM) or an equivalent volume of Intralipos. Seven minutes after adding the aggregating agent, the reaction was terminated by adding one-tenth volume of 100 mM EDTA, precooled to 0°C, and the suspension was immediately placed into an ice bath. The suspension was centrifuged at 10,000*g* at 4°C for 2 min to prepare platelet-free plasma, which was stored at −20°C until TXB_2 determination. The levels of TXB_2, a stable metabolite of TXA_2, in the platelet-free plasma were determined using a commercially available radioimmunoassay kit.

Assay of COX1 Activity

Because COX1 converts AA to PGG_2 and then to PGH_2, and this is finally converted to malonaldehyde in the presence of hemoglobin and reduced glutathione,[14] COX activity can be determined by measuring malonaldehyde formation.[15] Aliquots of a reaction mixture containing 100 mM tris/HCl (*p*H 8.0), 5 mM glutathione, 5 μM hemoglobin, and 10 U COX, together with 10–100 μM propofol or the equivalent volume of Intralipos, were preincubated at 37°C for 5 min before starting the reaction. The reaction was started by adding AA (to a final concentration of 0.5 mM) and terminated after incubation at 37°C for 1 min by adding 0.2 ml 100% trichloroacetic acid in 1 M HCl. After adding 0.2 ml 1% thiobarbiturate solution, the mixtures were placed into a boiling water bath for 20 min, then cooled to room temperature and centrifuged at 2,700*g* for 10 min. The absorbance of the clear supernatant at 532 nm was measured using a spectrophotometer (UV-visible recording spectrophotometer, UV-160A; Shimazu Corporation, Kyoto, Japan). A standard curve was constructed for malonaldehyde by adding known amounts of malonaldehyde to a reaction mixture with the aforementioned composition, except for the AA. Malonaldehyde formation was calculated using this standard curve.

Binding Assay

Propofol (100 μM) or an equivalent volume of Intralipos was added directly to test tubes containing 100 μl washed platelets and 700 μl buffer B. After incubation for 5 min at 37°C, a [^{3}H]-labeled TXA_2 receptor antagonist, 5Z-7-(3-endo-([ring-4-^{3}H] phenyl) sulphonylamino-[2.2.1.] bicyclohept-2-exo-yl) heptenoic acid ([^{3}H]-S145; 1–5 nM), was added and incubation continued at 37°C

Table 1. Summary of Aggregation Study

	40 μM Propofol		100 μM Propofol	
Agent	Intralipos	Propofol	Intralipos	Propofol
Epinephrine	63.8 ± 3.42	71.4 ± 5.14*	54.8 ± 5.15	26.3 ± 9.52†
ADP	77.5 ± 1.29	81.5 ± 2.64*	83.7 ± 1.50	27.7 ± 13.1†
Arachidonic acid	70.2 ± 3.40	77.5 ± 1.73†	84.2 ± 9.28	−1.0 ± 4.32†
PGG_2	ND	ND	53.2 ± 7.13	85.5 ± 19.8*
STA_2	70.6 ± 5.40	80.3 ± 8.88*	65.5 ± 3.51	90.5 ± 2.64†

Data are mean percent aggregation ± SD 7 min after stimulation. Light transmission of PPP containing equivalent volume of Intralipos was taken as 100%. ADP = adenosine diphosphate; PGG_2 = prostaglandin G_2; STA_2 = a thromboxane A_2 analog; ND = not done.

*$P < 0.05$, †$P < 0.01$ *versus* Intralipos (n = 5 each).

for 30 min. The reaction was terminated by adding 5 ml 5 mM Tris-HCl buffer (*p*H 7.4) that had been precooled to 0°C. Each mixture was then filtered *in vacuo* through a Whatman GF/C filter (Whatman International Ltd., Maidstone, United Kingdom) and washed three times with 5 ml precooled Tris-HCl buffer. The radioactivity on each filter (n = 5 each) was determined using a liquid scintillation analyzer (Tri-Carb 1900 CA; Packard Instrument Co., Meriden, CT). A zero control (without Intralipos) was also run to determine the effect of Intralipos alone.

Assay of IP_3 Formation

Aliquots of washed platelets (120 μl; counts 1,000,000/μl) were stimulated by STA_2 (final concentration of 1 μM, 30 μl) after preincubation at 37°C with propofol (30 and 100 μM) or an equivalent volume of Intralipos for 5 min. After stimulation for 5, 15, 30, and 60 s, the reaction was terminated by adding 50 μl ice-cold 10% perchloric acid solution. The samples were kept in an ice bath for 30 min and then centrifuged at 1,800*g* and 4°C for 10 min. The *p*H of the supernatant was adjusted to 7.5 with a solution of 1.53 M KOH and 75 mM HEPES. The samples were replaced in the ice bath for 30 min and then centrifuged at 8,000*g* and 4°C for 3 min. The IP_3 levels of the supernatants were measured using a commercially available IP_3 assay kit.

The drugs used were epinephrine hydrochloride (Sigma, St. Louis, MO), AA, malonaldehyde (Nacalai Tesque Co., Kyoto, Japan), 10% Intralipos, COX, and PGG_2 (Cayman Chemical Co., MI). ^{3}H-S145 was a gift from Shionogi Research Laboratories (Osaka, Japan), and STA_2 was a gift from Ono Pharmaceuticals (Osaka, Japan). Propofol was a gift from Zeneca Pharmaceuticals (London, United Kingdom). The radioimmunoassay kit was a thromboxane B_2 ^{3}H-assay system, code TRK 780 (Amersham International plc, Buckinghamshire, United Kingdom). The IP_3 assay kit was a D-myo-Inositol 1,4,5-triphosphate [^{3}H] assay system, code TRK.1000 (Amersham International plc).

All data are expressed as mean ± SD. Data of aggregation study and TXB_2 formation were analyzed using an unpaired *t* test. Data of COX activity, TXA_2 receptor-binding affinity, and IP_3 formations were analyzed using two-factor analysis of variance and Fisher's protected least significant difference. Differences at $P < 0.05$ were considered significant.

Results

Platelet Aggregation Study

Adenosine diphosphate (1–5 μM) and epinephrine (0.5–10 μM) induced both primary and secondary aggregation. Primary aggregation induced by ADP and epinephrine was not affected by propofol (1–100 μM). Secondary aggregation induced by them was enhanced by a low concentration (40 μM) but suppressed by a high concentration (100 μM) of propofol (fig. 1A and 1B). AA (1 mM)-induced aggregation was enhanced by 40 μM and completely abolished by 100 μM propofol (fig. 1C). PGG_2 (25 μM)-induced aggregation was enhanced by 100 μM propofol (fig. 1D). STA_2 (1 μM)-induced aggregation was enhanced by propofol (40 and 100 μM) (fig. 1E). Table 1 summarizes aggregation in percentages, i.e. the light transmission relative to that of PPP containing the equivalent volume of Intralipos, recorded 7 min after stimulation.

TXB_2 Formation

The TXB_2 level in the PRP supernatant was increased markedly by stimulation with ADP (1 μM), epinephrine (1 μM), AA (1 mM), and PGG_2 (25 μM). Propofol (40 μM) slightly suppressed ADP-, epinephrine-, and AA-induced

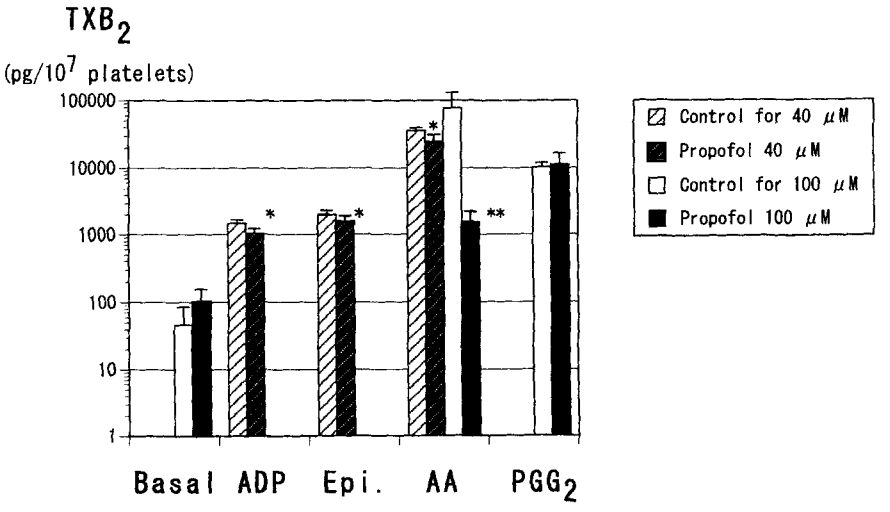

Fig. 2. Thromboxane B_2 (TXB_2) concentrations of platelets not stimulated (basal, n = 6 each) or stimulated (1 μM, n = 4 each) with adenosine diphosphate (ADP), epinephrine (Epi; 2 μM, n = 8 each), arachidonic acid (AA; 1 mM, n = 7 each), or prostaglandin G_2 (PGG_2; 25 μM, n = 6 each) in the presence of propofol (40 or 100 μM) or equivalent volume of Intralipos. Data are expressed as mean ± SD. *$P < 0.05$ and **$P < 0.01$ significantly different from that with equivalent volume of Intralipos.

TXB_2 formation, and 100 μM propofol suppressed AA-induced TXB_2 formation markedly. Propofol up to 100 μM did not affect PGG_2-induced TXB_2 formation (fig. 2).

COX1 Activity

Intralipos alone increased COX1 activity compared with zero control (control without Intralipos; fig. 3). Propofol (30 and 100 μM) suppressed COX1 activity compared with Intralipos alone, and 100 μM propofol suppressed the activity compared with zero control as well (fig. 3).

TXA_2 Receptor-Binding Affinity

Intralipos suppressed ^{3}H-S145 binding to platelets in a dose-dependent manner compared with the zero control (control without Intralipos). The effect of propofol (10–100 μM) on binding was not different from that observed with Intralipos alone (fig. 4).

IP_3 Formation

Inositol 1,4,5-triphosphate levels in resting platelets was 1.28 ± 0.52 and 2.41 ± 1.11 pmol/10^8 platelets, respectively, in the absence and presence of propofol (100 μM). The time course of IP_3 concentrations in platelets stimulated by STA_2 (1 μM) is shown in figure 5; the IP_3 level was significantly higher in the presence of propofol (30 and 100 μM) than with Intralipos alone (fig 5).

Discussion

The plasma concentrations of propofol at which 50% and 95% of patients do not respond to skin incision

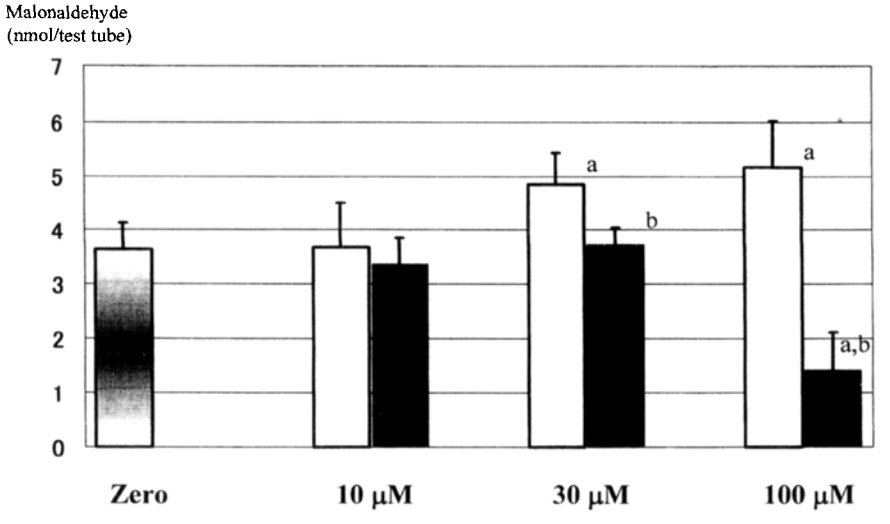

Fig. 3. Cyclooxygenase activity, in terms of malonaldehyde formation, in the presence of propofol (*black column*) or equivalent volume of Intralipos (*white column*). Zero control (*gradient-color column*) contained neither propofol nor Intralipos (n = 6 each). Data are expressed as mean ± SD. [a]$P < 0.01$ significantly different from that with zero control. [b]$P < 0.01$ significantly different from that with equivalent volume of Intralipos.

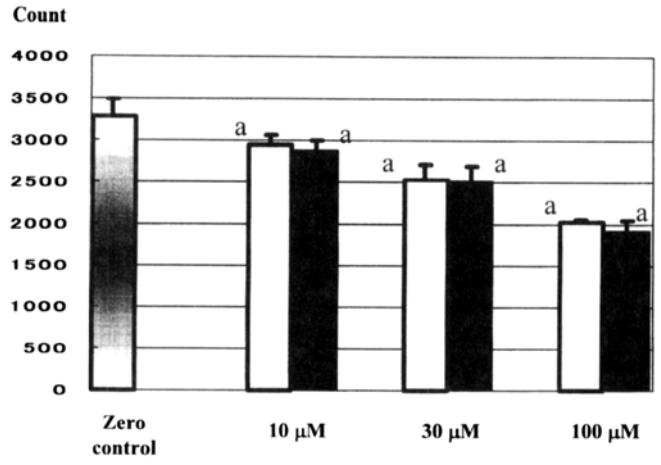

Fig. 4. Thromboxane receptor-binding affinity in the presence of propofol (*black column*) or equivalent volume of Intralipos (*white column*). Zero control (*gradient-color column*) contained neither propofol nor Intralipos (n = 5 each). Data are expressed as count of ^{3}H-S145 binding to platelets. $^aP < 0.01$ significantly different from that with zero control. There is no significant difference between the propofol and Intralipos groups.

(Cp_{50} and Cp_{95}, respectively) have been reported to be 85.4 and 153.9 μM (or 15.2 and 27.4 μg/ml), respectively.[16] Fentanyl administration decreases Cp_{50} markedly; fentanyl (1 ng/ml) decreased Cp_{50} by 63%.[16] Other investigators have shown that Cp_{50}s in the presence and absence of 67% N_2O were 30.1 and 45.5 μM (or 5.36 and 8.11 μg/ml), respectively.[17] However, because a large fraction of propofol exists in protein-bound form in plasma,[18] clinically relevant concentrations of propofol in protein-free buffer may be as low as 1 μM. Thus, our experiments using washed platelets are complicated by having an applied free concentration of high propofol, which is much higher than clinically relevant values. In contrast, in experiments performed in plasma, such as the aggregation study, clinically relevant anesthetic concentrations of propofol will exceed 30 μM, although sedative concentration of propofol will be lower. Thus, the present study indicates that propofol has different effects on platelet aggregation depending on concentration within a clinically relevant range; relatively high concentrations of propofol suppress platelet aggregation, whereas relatively low concentrations enhance aggregation. These complex effects of propofol have probably caused the inconsistency in the estimation of its effects on platelet aggregation by previous investigators.

Propofol altered secondary aggregation without altering primary aggregation when aggregation was induced by weak agonists such as epinephrine and ADP. The binding of these agonists to platelets activates phospholipase A_2 to release AA. This is then converted by COX1 to PGG_2 and finally to TXA_2 (fig. 6A), which plays a major role in the induction of secondary aggregation. Therefore, the alteration of secondary aggregation alone suggested that propofol affected the formation or function of TXA_2. The finding that 100 μM propofol inhibited AA-induced platelet aggregation completely, but significantly enhanced PGG_2- and STA_2 (a TXA_2 analog)-induced platelet aggregation, suggested that propofol suppresses the activity of COX1, the enzyme that converts AA to PGG_2. The level of TXB_2, a stable breakdown product of TXA_2, was radioimmunoassayed to estimate TXA_2 levels. In the absence of the anesthetic, the TXB_2 level did not differ much from those reported previously.[19,20] The finding that propofol suppressed AA-induced increase in TXA_2 but had no effect on PGG_2-induced TXA_2 increase further supports the concept that propofol suppresses COX1 activity. The inhibition of COX1 activity by propofol was confirmed finally by direct measurement of COX1 activity in a platelet-free system.

Propofol is water-insoluble and is now available commercially only dissolved in Intralipos (or Intralipid). Therefore, from the clinical standpoint, the net effect of propofol and Intralipos, not the effect of propofol alone, would be relevant. This study shows that Intralipos itself affects platelet modestly in a different way from that of propofol. Intralipos increased COX1 activity, and this effect was overcome only by a high concentration of propofol. It suggests that, in clinical use, the antiaggregatory effect of propofol may be ameliorated by the effect of Intralipos.

The finding that propofol augmented PGG_2- and STA_2-induced aggregations and, although only at a low concentration, augmented AA-induced aggregation suggested that, in addition to suppression of COX1 activity, propofol can augment TXA_2 responsiveness. The TXA_2 receptor is a member of the seven transmembrane domain family of receptors that interacts with G protein.[21] The G protein α subunit that links with this receptor is a member of the Gq family.[22] Platelets possess the β and γ forms of phospholipase C.[23] Phospholipase C-β is associated with G protein–linked receptors and can be activated by Gq.[23] Phospholipase C hydrolyzes phosphatidylinositol 4,5-bisphosphate and produces IP_3[24] (fig. 6B). This IP_3 formation is one of early processes of TXA_2-induced actions in platelets, and IP_3 thus formed mobilizes Ca^{2+} from intracellular stores to trigger aggregation and is then broken down quickly. In this study,

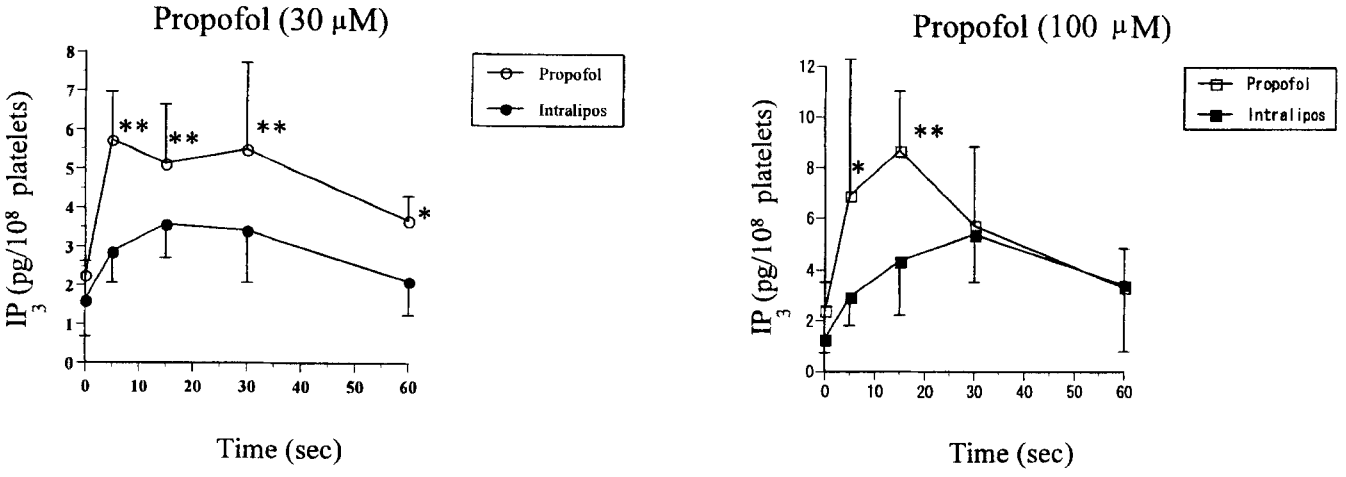

Fig. 5. Inositol 1,4,5-triphosphate (IP_3) formation in platelets after STA_2 stimulation in the presence of propofol (*open symbols*) or equivalent volume of Intralipos (*closed symbols*) (n = 5–8 each). Data are expressed as mean ± SD. IP_3 level was significantly higher than that before stimulation at 15–30 s with Intralipos alone and at 5–30 s with 30 or 100 μM propofol after the stimulation. *$P < 0.05$ and **$P < 0.01$ significantly different from that with equivalent volume of Intralipos.

we found that supraclinical concentrations (> 30 μM in plasma-free system) increase the STA_2-induced IP_3 production, which could contribute to the augmentation of platelet aggregation.

One possible explanation for these findings would be an increase in TXA_2 receptor-binding affinity. However, a receptor-binding assay using an isotope-labeled specific TXA_2 antagonist, ^{3}H-S145,[25,26] clearly ruled out this possibility, demonstrating that propofol itself does not alter the affinity and that, moreover, Intralipos suppresses it. The finding that propofol increased IP_3 levels in STA_2-stimulated platelets without affecting TXA_2 receptor-binding affinity can be explained by any of the three following mechanisms: enhancement of Gq protein, enhancement of phospholipase C activity, or suppression of IP_3 breakdown. At present we cannot speculate as to which of the aforementioned mechanisms underlies the enhancing effect of propofol on platelet aggregability. Furthermore, in clinical use, this effect of propofol is counteracted to some extent by the Intralipos-mediated decrease in ligand affinity.

Backwell *et al.*[27] showed that general anesthesia with propofol decreased blood loss compared with conventional inhaled agents during endoscopic sinus surgery.

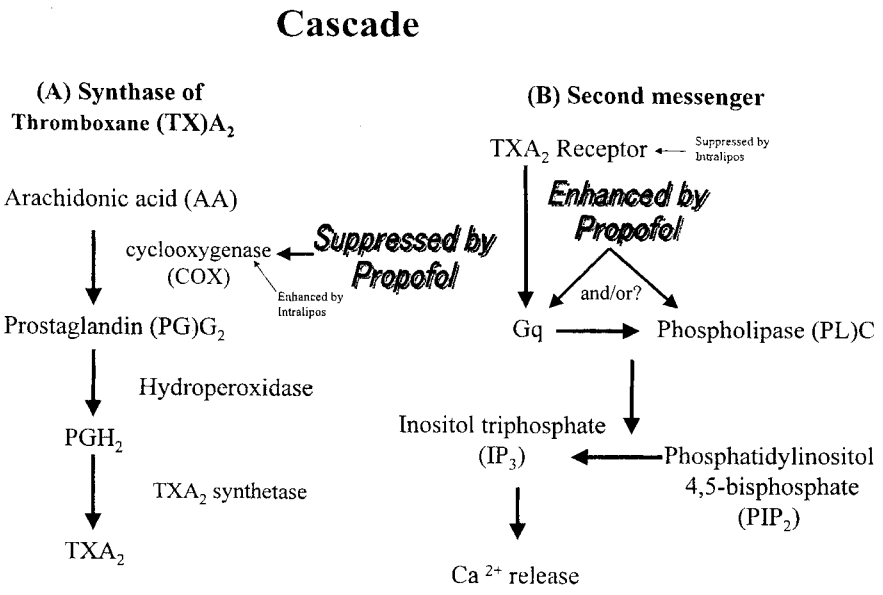

Fig. 6. (*A*) The thromboxane synthetic pathway. The site that propofol affects is indicated by "suppression" and an arrow. (*B*) The mechanism underlying thromboxane A_2 (TXA_2)-mediated platelet activation. The expected site(s) propofol may affect are indicated by "enhancement" with two arrows.

Although such clinical results may be coincidental because of a variety of factors, it does suggest the need for further well-controlled clinical studies documenting the effects of varying anesthetic agents in platelet function and bleeding.

We conclude that, *in vitro*, propofol has both suppressive and enhancing effects on platelet aggregation, and that the suppressive effect is caused by the suppression of COX1 activity, whereas the enhancing effect is caused by increased IP_3 formation.

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