The treatment of propofol induced the TGF-β1 expression in human endothelial cells to suppress endocytosis activities of monocytes

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1. Introduction

Propofol (2,6-diisopropylphenol) is one of the most popular agents used to induce anesthesia in surgical procedures for long-term sedation and to treat postoperative nausea in critically-ill patients [1–3]. It is known that propofol could affect the immune system in numerous ways. In clinical studies, propofol decreased necrophagocytosis and microbicidal activity, but increased tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) gene expression in patient alveolar macrophages [4,5]. In laboratory studies, propofol inhibited immunological activities of isolated human neutrophils as well as the migratory activity of isolated human leucocytes through an endothelial cell monolayer [6,7]. Furthermore, propofol enhanced lipopolysaccharide (LPS)-stimulated TNF-α and IL-1β but reduced LPS-stimulated IL-8 expression [8,9]. However, propofol also reduced LPS-induced expression of CD14, while HLA-DR expression was unaffected [10]. There is no mechanism explaining the contradictory effects of propofol on the immune regulation and inflammation induced by LPS.

To date, no studies have addressed the correlations between propofol and TGF-β1 expression. It is known that TGF-β1 regulates immune processes in vivo and that overproduction of TGF-β1 may be associated with immune suppression. TGF-β1 has been considered one of the major cytokines capable of suppressing T cell proliferation and macrophage activation [11–13]. In mammalian cells, the presence of TGF-β1 is required for the proper folding and secretion of TGF-β1 which is non-covalently associated with the pro-domain (latency-associated peptide, LAP) in a "latent" form. In this form, TGF-β1 is unable to bind receptors until it is activated, becoming the mature 25 kD form of TGF-β1. Activation of latent TGF-β1 has been studied extensively in vivo; altered pH, heat, proteases or chemotropic agents have all been shown to release active TGF-β1 from the latent complex [14,15].

In this study, we examined the effects of propofol treatment on total and active TGF-β1 levels in patient sera. We found that...
human peripheral blood mononuclear cells, lymphocytes, monocytes and vein endothelial cells responded to propofol treatment, expressing the TGF-β1 in vitro. We also evaluated the immunomodulatory activity of propofol-induced TGF-β1 expression on monocyte endocytosis. Our results indicated that propofol could induce endothelial cells to produce latent TGF-β1 and enhance the ability of PBMCs to convert it into its active form. Moreover, propofol-induced TGF-β1 expression in patient sera suppressed monocyte endocytosis.

2. Material and methods

2.1. Patient and methods

The study was approved by the Human Research Ethics Committee of the Tzu Chi Medicine Center Hospital, Hualien, Taiwan. Sera from 32 trauma patients or healthy volunteers and heparinized white blood cell concentrates from three healthy volunteers were obtained after receiving institutional approval and written informed consent from the participants. All medical procedures followed the standard guidelines. Sera from patients, who were randomly selected according to age, sex, department, diagnosis and operations (Table 1), were collected within 48 days of surgical operation and divided into two groups. Eight trauma patients were excluded due to co-administration of other anesthetics during the experimental period. Propofol-treated individuals received a daily intravenous injection of propofol for a minimum of 2 days ($n = 14$). Untreated individuals did not receive any intravenous injection of propofol ($n = 10$).

2.2. Cell lines

THP-1 and Jurkat cells were obtained from the Bioresource Collection and Research Center, Hsinchu, Taiwan. Primary cultures of HUVECs were kindly provided by Dr. Ko-Jiunn Liu (Nation Health Research Institute, Chunan, Taiwan). HUVECs were grown in 199 Medium (Gibco, Invitrogen Co., Grand Island, NY) supplemented with 20% fetal bovine serum, 25 units/ml heparin (Sigma, St. Louis, MO) and 30 μg/ml endothelial cell growth supplements (Sigma), according to the instructions of the American Type Culture Collection, Manassas, VA. Cells from passages 3 to 7 were used for experiments.

2.3. Human peripheral blood mononuclear cells isolation

Human peripheral blood mononuclear cells were separated from white blood cell concentrates of healthy donors by Ficoll–Paque PLUS (GE Healthcare, Chicago, IL). The process is described briefly below. Fresh human white blood cell concentrates (pretreated with anticoagulant) were mixed with the same volume of PBS. Then, the diluted blood samples were carefully layered on Ficoll–Paque PLUS and centrifuged at 2000 rpm for 20 min at 18 °C. The upper layer was drawn off carefully. The white layer (mainly lymphocytes) and yellow Ficoll–Paque PLUS layer (contained monocytes and neutrophils) were carefully transferred to a clean centrifuge tube without contaminating the lower layer. A minimum of three volumes of PBS were added to gently suspend the cells followed by centrifugation at 405 g for 10 min at 18 °C. The supernatant was removed and the cells were washed again with PBS. Finally, the cells were suspended in RPMI 1640 (with 10% FBS and 1% PSA) for the study.

2.4. Human TGF-β1 measurement

Human peripheral blood mononuclear cells, Jurkat and THP-1 cells were seeded at a density of 2 × 10^6 cells in 1 ml growth medium. Each culture was co-incubated with propofol for 24 h at final concentrations of 0.45, 2 and 6.5 μg/ml, which approximate the

Table 1

The patients were randomly selected with different ages, sex, department, diagnosis, and operation from the Tzu Chi Medicine Center Hospital, Hualien, Taiwan. “PS: plastic surgery; CVS: cardiovascular; GS: general surgery; NS: neurosurgery and CS: chest surgery”. +: represents that the patient received propofol during care medication.

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<th>No.</th>
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<td>5</td>
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<td>Right intracranial hemorrhage</td>
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<td>41</td>
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maximum therapeutic dosages of propofol for postoperative nausea and vomiting [3], for sedation [2], and for anesthesia [1,16], respectively. HUVECs (3 × 10⁵ cells, 600 µl) were seeded in a gelatin-coated plate and co-incubated with 6.5 µg/ml propofol. After 24 h incubation, supernatants were collected (Day 1 group) or the same amount of propofol was added again and the supernatants were collected after incubating for another 24 h (Day 2 group).

Human TGF-β1 in culture supernatants and human sera was measured by TGF-β1 Emax ImmunoAssay System (Promega, Madison, WI) as per the manufacturer’s instructions. Briefly, human sera were diluted in PBS and sample buffer. Cell culture supernatants were not diluted. Samples were acidified to approximately pH 2.6 with 1 M HCl and then neutralized to approximately pH 7.6 with 1 M NaOH to measure the total TGF-β1. Amounts of active TGF-β1 were measured without acidification.

2.5. Endocytosis activity measurement

THP-1 cells (3 × 10⁵ cells, 300 µl) were seeded in RPMI 1640 without FBS and 300 µl HUVEC-conditioned medium from the Day 2 group was added for 16 h. Co-culturing HUVEC-conditioned medium without propofol treatment served as the control group, while co-culturing HUVEC-conditioned medium with propofol (6.5 µg/ml) served as the propofol group. Cells were harvested and centrifuged (405g, 4 ℃, 5 min). The supernatant was discarded and 180 µl fresh medium was added to resuspend the cells. The cells were pre-cooled at 0 °C for 5 min and then co-incubated with dextran-fluorescein isothiocyanate solution (dextran-FITC, 1 mg/ml) at 0 or 37 ℃ for 2 h. The cells were washed with PBS three times and analyzed by flow cytometry (BD Biosciences, San Diego, CA). Dextran-FITC uptake was represented as the total FL-1 fluorescence intensity. However, total FL-1 fluorescence intensity at 0 ℃ was considered to be nonspecific dextran-FITC uptake and was subtracted. Thus, specific dextran-FITC uptake of each sample was expressed as the total FL-1 fluorescence intensities at 37 ℃ minus total FL-1 fluorescence intensities at 0 ℃. Relative endocytosis activity = (specific dextran-FITC uptake of sample/specific dextran-FITC uptake of control) × 100.

Patient sera from each group (propofol-treated and control) were mixed. 3 × 10⁵ THP-1 cells were seeded and cultured in different conditions for 16 h as described below: (a) Control group: THP-1 cells were cultured in 600 µl serum-free RPMI 1640. (b) SB431542 group: THP-1 cells were cultured in 600 µl serum-free RPMI 1640 with 15 µM SB431542 (Sigma, Louis, MO). (c) Propofol group: THP-1 cells were cultured in 300 µl serum-free RPMI 1640 mixed with 300 µl human sera from propofol-treated patients. (d) Propofol SB431542 group: THP-1 cells were cultured in 300 µl serum-free RPMI 1640 mixed with 300 µl human sera from propofol-treated patients and 15 µM SB431542. (e) Untreated group: THP-1 cells were cultured in 300 µl serum-free RPMI 1640 mixed with 300 µl human sera from untreated patients. (f) Untreated SB431542 group: THP-1 cells were cultured in 300 µl serum-free RPMI 1640 mixed with 300 µl human sera from untreated patients and 15 µM SB431542. Then, the relative endocytic activity was assayed as described above.

2.6. Statistical analysis

All data are expressed as means ± SE. When measuring human TGF-β1 expression in patient sera, the sample size consisted of 14 propofol-treated patients and 10 untreated patients; each sample was measured using two independent ELISAs. The Kruskal–Wallis test was used to compare differences between groups. All other in vitro data were compared using Student’s t-test. Data regarding TGF-β1 expression in human peripheral blood mononuclear cells exposed to conditioned medium were obtained from two independent experiments and duplicated in each group (n = 4). Data regarding TGF-β1 expression in Jurkat, THP-1 and HUVEC exposed to conditioned medium were obtained from three independent experiments and duplicated in each group (n = 6). Data regarding pinocytic activity of THP-1 cells co-cultured with conditioned HUVEC medium were obtained from two independent experiments and duplicated in each group (n = 4). Data regarding pinocytic activity of THP-1 cells co-cultured with patient sera were obtained from three independent experiments and duplicated in each group (n = 6). Statistical significance was set at p < 0.05.

3. Results

3.1. Intravenous injection of propofol during medical procedures increased levels of both total and active TGF-β1 in patient sera

In order to study the immunoregulatory effects of propofol, we assessed the effect of propofol treatment on the expression of the inhibitory cytokine TGF-β1. Sera from randomly-selected trauma patients (Table 1) in Tzu Chi Medicine Center Hospital were obtained and the expression of TGF-β1 was measured. All medical procedures followed standard guidelines. Sera from patients with different diseases and medical processes were collected daily for two consecutive days after surgery and divided into two groups according to whether or not the patients had intravenous injections of propofol (n = 14) or not (n = 10). Results showed that propofol injections significantly increased total amounts of TGF-β1 in patient sera compared to untreated controls (Fig. 1A). In addition, levels of active TGF-β1 also increased significantly during the first and second days of propofol injection (Fig. 1B). Moreover, levels of total and active TGF-β1 in sera from healthy donors (n = 8) were also determined; the concentrations were 28.62 ± 3.29 ng/ml for total TGF-β1 and 0.530 ± 0.016 ng/ml for active TGF-β1 (results not shown). According to these results, clinical propofol administration could increase expression of both total and active TGF-β1 in patients after surgery.

3.2. Clinical dosages of propofol did not have significant effects on total TGF-β1 expression in human peripheral blood mononuclear cells

To verify which type of cells can increase the production of TGF-β1 following intravenous injections of propofol, human peripheral blood mononuclear cells (PBMCs) were tested for their ability to express TGF-β1 by direct in vitro propofol treatment. The results showed that propofol did not affect total TGF-β1 levels at all (Fig. 2A), whereas a minor increase was observed (Fig. 2B) following treatment with 6.5 µg/ml propofol.

3.3. Clinical dosages of propofol slightly reduced levels of total TGF-β1 but increased levels of active TGF-β1 in conditioned media from Jurkat and THP-1 cells

Because human PBMCs contain different types of immune cells, human T lymphocytes (Jurkat cells) were first tested to determine whether they can convert latent TGF-β1 into its active form following propofol stimulation. The results showed that total amounts of TGF-β1 were not significantly changed following treatment with 0.4 or 2 µg/ml propofol, but were slightly reduced following treatment with 6.5 µg/ml propofol (Fig. 3A). Similar to the PBMC findings, we found that the amounts of active TGF-β1 in Jurkat-conditioned media were also slightly increased following 6.5 µg/ml propofol treatment (20.85 ± 3.24 pg/ml compared to 13.13 ± 4.2 pg/ml in the control group) (Fig. 3B).

Additionally, human monocytic THP-1 cells were also further investigated to determine whether propofol could affect TGF-β1 expression in these cells. Similar to Jurkat cells, our results showed
that the total amounts of TGF-β in THP-1-conditioned media were decreased and the levels of active TGF-β1 were increased (Fig. 4). In contrast to Jurkat cells, our results showed that propofol treatment increased the levels of active TGF-β1 in a dose-dependent manner.

3.4. Propofol induced the expression of latent, but not active, TGF-β1 in human umbilical vein endothelial cells

To determine which type of cell was associated with latent TGF-β1 induction following intravenous propofol injection, human blood vessel endothelial cells were tested. Because 6.5 μg/ml propofol had significant effects in earlier experiments, HUVECs were therefore treated with 6.5 μg/ml propofol, and the results showed that propofol increased the total TGF-β1 expression on Day 1 and Day 2 groups compared to the control group, respectively (Fig. 5A). However, changes in the levels of active TGF-β1 were not significant in the Day 1 and Day 2 groups compared to the control group, respectively (Fig. 5B). Thus, we suggest that propofol induces latent TGF-β1 secretion but did not affect TGF-β1 activation in human vein endothelial cells.

3.5. Propofol-induced TGF-β1 has inhibitory effects on the endocytosis of monocytic THP-1 cells

To verify whether propofol-treated, HUVEC-conditioned media has immunological activity, the endocytic activity of THP-1 cells was assessed by dextran-FITC uptake as described above. The results showed that the propofol-treated, HUVEC-conditioned medium inhibited the endocytic activity of THP-1 cells by about 18% (Fig. 6).

Finally, to confirm whether propofol-induced TGF-β1 expression could inhibit endocytic activities of monocytes, patient sera from each group (with or without propofol treatment) were mixed. After co-culture with propofol-treated patient sera, endocytic activity of THP-1 cells was significantly reduced in the propofol-treated group compared to the control group, but the endocytic activity of THP-1 cells was not significantly reduced in the untreated group compared to the controls. However, addition of SB431542, a potent inhibitor of TGF-β receptor-associated kinase ALK-5 [17], resulted in dramatic recovery of endocytic activity in the propofol group. However, endocytic activities were unchanged with or without SB431542 in the untreated group. In addition, no significant difference was found between the untreated and the control groups, suggesting that sera from propofol-treated patients inhibited the endocytic activity of monocytes ex vivo due to the contributions of TGF-β1.

4. Discussion

In this study, we found that both latent and active TGF-β1 were induced by clinical doses of propofol in human sera (Fig. 1). This induction was mediated by two different mechanisms. First, propofol induced endothelial cells to secrete increased levels of latent
TGF-β1 (Fig. 5); second, propofol induced T lymphocytes (Fig. 3) and monocytes (Fig. 4) to activate the surrounding latent TGF-β1.

Inhibition of the TGF-β pathway using the inhibitor SB431542 indicated that propofol-induced TGF-β1 in patient sera mediated suppression of monocyte endocytosis in vitro (Fig. 7). Monocytes mediate many innate immune responses. Reducing the endocytic activity of monocytes and macrophages might have negative effects on antigen uptake, presentation and immune activation. In addition, it seems that propofol-induced TGF-β1 could inhibit or downregulate phagocytosis, production of reactive nitrogen intermediates, TNF-α expression, common γ-subunit expression and TLR signaling pathways in monocytes [13,18,19]. Thus, the inhibitory activities of TGF-β1 on monocytes may play a key role in suppressing inflammatory responses after clinical administration of propofol.

There are two arguments about the effect of propofol on immune activity. First, there are conflicting conclusions about the effect of propofol on LPS-induced inflammatory responses. Propofol could attenuate CD14 expression on the surface of LPS-stimulated monocytes to reduce inflammatory responses [10]. In addition, propofol also protects endothelial cells against LPS-induced barrier dysfunction by inhibiting NF-κB activation [20]. However, propofol also was reported to reinforce the effects of LPS-induced proinflammatory cytokines, including TNF-α and IL-1β, which induce or enhance inflammatory responses through NF-κB activation [8,21,22]. Based on our findings, the bioactive TGF-β1 induced by propofol might help to explain the controversial effects of propofol found in previous literature. Studies had shown that propofol can increase the LPS-stimulated proinflammatory cytokine expression by activating the NF-κB pathway; this might be caused by the transient effects of propofol-induced TGF-β1 on NF-κB activation [21,23]. However, TGF-β1 is a multifunctional cytokine and has been reported to decrease NF-κB activity with or without LPS stimulation [24,25]. Thus, the controversial effects of propofol might be due to TGF-β1 induction. Propofol could induce secretion of latent TGF-β1 and enhance conversion of latent TGF-β1 into its active form. Consequently, differences in dosage, target cells, and cell
Culture conditions would affect the synergistic effect of propofol-induced TGF-β1 and result in different experimental outcomes.

A secondary controversial phenomenon is the effect of propofol on immune cell activity. Although many proinflammatory cytokines, such as TNF-α, which could increase the activities of granulocytes and monocytes are induced by propofol [26], propofol treatment was found to downregulate the activities of many human immune cells, including leukocytes, lymphocytes, monocytes, macrophages and neutrophils in many laboratory studies and clinical observations [4,6,7,10,27,28]. Our findings could provide possible explanations to these studies. Prolonged existence of propofol in the sera could induce endothelial cells to produce latent TGF-β1 and enhance the ability of PBMCs to convert latent TGF-β1 into its active form. Thus, propofol-induced proinflammatory cytokines may be counteracted by continuous production of latent and active TGF-β1 [29–31]. Such a mechanism could explain the suppressive effect of propofol on immune function among surgical or general care patients.

Thus, our results in this study should be valuable for patients receiving propofol treatment during medical operations, as their innate immunity could be compromised due to propofol-induced active TGF-β1. On the disadvantageous side, these patients could be more susceptible to opportunistic infections by certain pathogens, such as Staphylococcus aureus, due to the immunosuppressive...
effects of TGF-β1. However, these patients would have a lower risk of death as a result of endotoxin sepsis due to of propofol’s antagonistic effects on TNF-α [32].

In addition to immune regulation, TGF-β1 also plays a crucial role in the inhibition of macrophage activation, suppression of the inflammatory response, and the induction of immune tolerance. TGF-β1 is characterized by strong anti-inflammatory effects, which include inhibition of NF-κB activation and the secretion of pro-inflammatory cytokines. TGF-β1 also suppresses the synthesis of pro-inflammatory cytokines, such as TNF-α and IL-1, and promotes the expression of anti-inflammatory mediators, such as IL-10, which can help to dampen the immune response and promote tissue repair.

References