High-dose fentanyl has been widely used as a general anesthetic for patients undergoing heart surgery. Fentanyl administered intravenously at the clinical dose (4.5 \(\mu g\)/kg) has been shown to slightly decrease systemic blood pressure and vascular resistance, whereas high doses (40-160 \(\mu g\)/kg) have been shown to significantly decrease mean peripheral blood pressure. In addition, the hypotension produced by high-dose fentanyl (75 \(\mu g\)/kg) is associated with an increased need for the use of alpha-adrenergic agonists to maintain blood pressure. Fentanyl has been shown to inhibit the \(\alpha_1\)-adrenoceptor agonist-induced contraction in isolated aorta and pulmonary arteries. The \(\alpha_1\)-adrenoceptors are a heterogeneous group of receptors and, based on radioligand binding, molecular biology and isolated tissue experiments, they have been classified into three subtypes: the \(\alpha_{1A}\)-, \(\alpha_{1B}\)- and \(\alpha_{1D}\)-adrenoceptors for native receptors. All three subtypes of the \(\alpha_1\)-adrenoceptors have a high affinity for the nonsubtype-selective \(\alpha_1\)-adrenoceptor antagonist prazosin, and are expressed in the rat aorta.
vascular smooth muscles, including the rat aorta. These subtypes can be identified by selective and non-selective antagonists. For example, 5-methyl-urapidil (5-MU) has a 10 to 50 times higher affinity for \( \alpha_{1D} \)-adrenoceptors, and the affinity of BMY 7378 for \( \alpha_{1D} \)-adrenoceptors is at least 100-fold higher. Chloroethylclo-nidine (CEC) is an irreversible antagonist that preferentially inactivates \( \alpha_{1D} \)-adrenoceptors, but it can also partially inactivate \( \alpha_{1D} \)-adrenoceptors. The \( \alpha_{1D} \)-adrenoceptors mediate the phenylephrine-induced contraction of the rat abdominal aorta, thoracic aorta, and mesenteric artery, and \( \alpha_{1D} \)-adrenoceptors mediate the phenylephrine-induced contraction of the human umbilical vein and canine pulmonary artery, as well as phenylephrine-induced contraction in the dog aorta.

However, to the best of our knowledge, the \( \alpha_{1D} \)-adrenoceptor subtype that is involved in the fentanyl-induced attenuation of the phenylephrine contraction-response curve in systemic circulation such as rat aortas has not yet been identified. The goals of the current in vitro study were to identify the \( \alpha_{1D} \)-adrenoceptor subtype that is involved mainly in the fentanyl-induced attenuation of phenylephrine-induced contraction in isolated endothelium-denuded rat aorta and to characterize the \( \alpha_{1D} \)-adrenoceptor subtype that is functionally important in mediating the contractile response to phenylephrine.

**MATERIALS AND METHODS**

All experimental procedures and protocols were approved by the Institutional Animal Care and Use Committee. Sprague-Dawley male rats, weighing 250-350 g each, were anesthetized by the intraperitoneal administration of pentobarbital sodium (50 mg/kg). The descending thoracic aorta was dissected free, and the surrounding connective tissue and fat were removed under microscopic guidance while the blood vessels were bathed in Krebs solution of the following composition: 118 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO\(_4\), 1.2 mM KH\(_2\)PO\(_4\), 2.4 mM CaCl\(_2\), 25 mM NaHCO\(_3\), 11 mM glucose and 0.03 mM EDTA. The aorta was then cut into 2.5-mm rings, which were suspended on Grass isometric transducers (FT-03, Grass Instrument, Quincy, MA, USA) with a 2.0 g resting tension in 10 mL temperature-controlled baths (37°C) containing the Krebs solution, which was continuously gassed with 95% O\(_2\) and 5% CO\(_2\). The rings were equilibrated at a 2.0 g resting tension for 120 min, during which time the bathing solution was changed every 15 min. In all rings, the endothelium was intentionally removed by inserting a 25-G needle tip into the lumen of the rings and gently rolling the rings for a few seconds. The contractile response induced by isotonic 60 mM KCl was measured in each of the aortic rings.

**Experimental protocol**

The first series of these experiments was aimed at assessing the effect of fentanyl on contractile response induced by the \( \alpha_{1D} \)-adrenoceptor agonist phenylephrine in endothelium-denuded rings. Fentanyl was added directly to the organ bath 30 min before cumulative phenylephrine-induced contraction. The effect of fentanyl on the concentration-response curves for phenylephrine (10\(^{-9}\) to 10\(^{-4}\) M) was assessed by comparing the contractile response in the presence or absence of fentanyl (3 \times 10\(^{-5}\), 10\(^{-4}\), 3 \times 10\(^{-4}\) M).

The second series of experiments was designed to determine which subtype of \( \alpha_{1D} \)-adrenoceptor is functionally important in mediating phenylephrine-induced contraction in endothelium-denuded rat aorta. The effect of subtype-selective \( \alpha_{1D} \)-adrenoceptor antagonists (\( \alpha_{1D} \)-adrenoceptor antagonist: 3 \times 10\(^{-5}\), 10\(^{-4}\), 3 \times 10\(^{-4}\) M 5-MU; \( \alpha_{1D} \)-adrenoceptor antagonist: 3 \times 10\(^{-8}\), 10\(^{-7}\), 3 \times 10\(^{-7}\) M BMY 7378) on the concentration-response curve for phenylephrine was assessed by comparing each contractile response in the presence and absence of each subtype-selective \( \alpha_{1D} \)-adrenoceptor antagonist. The incubation period for each subtype-selective \( \alpha_{1D} \)-adrenoceptor antagonist was 30 min before phenylephrine-induced contraction.

The third series of experiments was designed to assess the effect of the irreversible \( \alpha_{1D} \)-adrenoceptor antagonist CEC on the concentration-response curve for phenylephrine. The first concentration-response curve for phenylephrine was constructed before pretreatment with 10\(^{-7}\) M CEC. After being washed, aortic rings were exposed to CEC (10\(^{-7}\) M) for a period of 20 min. Following removal of the CEC by exchanges of the Krebs solution every 10 min for 1 hour, a second concentration-response curve for phenylephrine was constructed.

In the fourth series of experiments, the \( \alpha_{1D} \)-adrenoceptor subtype dependence of fentanyl-induced attenuation of the contractile response induced by phenylephrine was examined. The effect of fentanyl (10\(^{-6}\) M) on the concentration-response curve for phenylephrine in the rings which had been pretreated with either 10\(^{-7}\) M 5-MU or 3 \times 10\(^{-4}\) M BMY 7378 was assessed by comparing the contractile response in the presence and absence of fentanyl (10\(^{-6}\) M). In addition, the role of the \( \alpha_{1D} \)-adrenoceptor in the fentanyl-induced attenuation of the contractile response induced by phenylephrine was assessed by examining the phenylephrine (10\(^{-4}\) to 10\(^{-1}\) M) concentration-response curve after prazosin (3 \times 10\(^{-4}\) M) was added directly to organ bath, either alone or in combination with fentanyl (3 \times 10\(^{-4}\) M). The incubation period for the subtype-selective or non-subtype-selective \( \alpha_{1D} \)-adrenoceptor antagonists (3 \times 10\(^{-4}\) M prazosin, 10\(^{-4}\) M 5-MU and 3 \times 10\(^{-4}\) M BMY 7378) plus fentanyl (10\(^{-6}\), 3 \times 10\(^{-4}\) M) or \( \alpha_{1D} \)-adrenoceptor antagonist (subtype-selective or non-subtype-selective) alone was 30 min before the phenylephrine-induced contraction.
Drug and solution
All drugs used in the present study were of the highest purity commercially available and included phenylephrine HCl, acetylcholine, prazosin, 5-MU, CEC, BMY 7378 (8-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspiro[4.5]decane-7,9-dione dihydrochloride) (Sigma Chemical, St. Louis, MO, USA), and fentanyl (Hana Pharmaceutical Co., Ltd., Seoul, Korea). All concentrations are expressed as the final molar concentration in the organ bath. All drugs were dissolved in distilled water.

Data analysis
The values are expressed as means ± SD. Contractile responses to phenylephrine are expressed as a percentage of their own maximum contraction to isotonic 60 mM KCl. The first and second phenylephrine-induced contractions are expressed as a percentage of the maximum obtained from the first phenylephrine concentration-response curve. The logarithm of the drug concentration (ED50), eliciting 50% of the maximum contractile response, was calculated using nonlinear regression analysis by fitting the concentration-response relation for phenylephrine to a sigmoidal curve, by using commercially available software (Prism version 3.02: GraphPad software, San Diego, CA, USA). Data were fitted to a sigmoidal dose-response curve using the following algorithm Y = Bottom + (Top - Bottom)/(1 + 10^((LogED50 - X) × Hill Slope)). The concentration ratio (CR) is defined as the concentration of agonist required to induce 50% maximal contractile response in the presence of antagonist divided by the agonist concentration that elicits the same degree of response in the absence of antagonist. The pA2 value represents the concentration of antagonists necessary to displace the concentration-response curve of an agonist by twofold. Subtype-selective α1-adrenoceptor antagonist pA2 values (-log M) were calculated from Arunlakshana and Schild plots and were obtained from the X-intercept of the plot of log (CR-1) against log molar antagonist concentration, where the slope was not different from unity.13 The slope and pA2 values calculated from Arunlakshana and Schild plots are expressed as mean ± SEM.13 Statistical analysis was performed using Student’s t-test for paired comparison. One-way analysis of variance, followed by Tukey’s multiple comparison, was used to compare more than two means. The p value < 0.05 was considered significant.
significant. N refers to the number of rats whose descending thoracic aortic rings were used in each experiment. Each group contained at least two rings from the same rat.

## RESULTS

Fentanyl (3 × 10⁻⁷ M) did not significantly alter the phenylephrine concentration-response curve (Fig. 1). However, higher concentration of fentanyl (10⁻⁶, 3 × 10⁻⁶ M) significantly attenuated (p < 0.05 versus no drug) phenylephrine-induced contraction (ED₄₀: no drug; -8.41 ± 0.34 versus 10⁻⁶ M fentanyl; -7.84 ± 0.29, 3 × 10⁻⁶ M fentanyl; -7.70 ± 0.28) in endothelium-denuded rat aorta (Fig. 1). Treatment of the aorta with 5-MU (3 × 10⁻⁸, 10⁻⁷, 3 × 10⁻⁷ M) caused a parallel rightward shift (p < 0.01 versus no drug) in the phenylephrine concentration-response curve (ED₄₀: no drug; -8.26 ± 0.19 versus 3 × 10⁻⁷ M 5-MU; -7.81 ± 0.13, 10⁻⁷ M 5-MU; -7.23 ± 0.26, 3 × 10⁻⁷ M 5-MU; -6.82 ± 0.15) in a concentration-dependent manner (Fig. 2A). Analysis of the data using an Arunlakshana and Schild plot for the antagonism of phenylephrine-induced contraction by 5-MU yielded a slope (1.21 ± 0.23) that was not significantly different from unity (Fig. 2B). The pA₂ value for 5-MU at a concentration of 10⁻⁷ M which is close to the reported affinity (8.7-8.1) for the α₁A-adrenoceptor, suggesting that the α₁A-adrenoceptor plays a primary role in phenylephrine-induced contraction of the rat aorta.

Fentanyl (3 × 10⁻⁶ M) produced a parallel rightward shift (p < 0.01 versus no drug) in the phenylephrine concentration-response curve (ED₄₀: no drug; -8.26 ± 0.30 versus 3 × 10⁻⁶ M BMY 7378; -7.63 ± 0.19, 10⁻⁴ M BMY 7378; -7.32 ± 0.23, 3 × 10⁻⁵ M BMY 7378; -6.92 × 0.14) in a concentration-dependent manner (Fig. 3A). The Arunlakshana and Schild plot for antagonism of phenylephrine-induced contraction by BMY 7378 yielded a slope (0.87 ± 0.19) that was not significantly different from unity (Fig. 3B). The pA₂ value for BMY 7378 was 8.99 ± 0.24 (Fig. 3B), which is close to the reported affinity (8.7-8.1) for the α₁D-adrenoceptor, suggesting that the α₁D-adrenoceptor plays a primary role in phenylephrine-induced contraction of the rat aorta.

CEC (10⁻⁴ M) produced 72.9% inhibition of the first phenylephrine-induced maximal contraction (p < 0.0001 versus no drug) (Fig. 4), which suggests that phenylephrine-induced contraction in the rat aorta involves the CEC-sensitive α₁D-adrenoceptor subtype (α₁D- and α₁A-adrenoceptors).

Comparison with aortic rings not treated with fentanyl showed that fentanyl (10⁻⁷ M) significantly attenuated (p < 0.01 versus 5-MU alone) phenylephrine-induced contraction (ED₄₀: 10⁻⁵ M 5-MU; -8.10 ± 0.24 versus 10⁻⁵ M 5-MU + 10⁻⁶ M fentanyl; -7.72 ± 0.24) in rings pretreated with 5-MU at a concentration of 10⁻⁶ M which is close to the reported affinity (9.3-8.4) for the α₁D-adrenoceptor (Fig. 5). In rings pretreated with BMY 7378 at 3 × 10⁻⁷ M concentration which is close to the reported affinity (8.7-8.1) for the α₁D-adrenoceptor, fentanyl (10⁻⁶ M) did not significantly alter phenylephrine-induced contraction as compared with rings not treated with fentanyl (Fig. 6).

Fentanyl (3 × 10⁻⁶ M) had no effect on phenylephrine-induced contraction of rings pretreated with prazosin (3 × 10⁻⁸ M) (Fig. 7).
phenylephrine-induced maximal contraction (phenylephrine-induced maximal contraction: 100% = 3.9 ± 0.16 g [n = 4] for the rings with no drug).

**DISCUSSION**

Despite widespread use of fentanyl in patients undergoing heart surgery, we believe that this is the first study to show that fentanyl attenuates phenylephrine-induced contraction by inhibiting the cellular signal transduction pathway involved in the α1-adrenoceptor-mediated contraction of the rat aortic smooth muscle. The α1-adrenoceptor exerts a great influence on modulation of contraction induced by phenylephrine in rat aortic smooth muscle.

Fentanyl attenuates phenylephrine-induced contraction in the canine pulmonary artery by binding to the α1-adrenoceptor, and attenuates also the α1-adrenoceptor agonist (phenylephrine and norepinephrine)-induced dose-response curve by an alpha-adrenergic blocking action in isolated rabbit and rat aorta. Consistent with previous studies, fentanyl (10⁻⁶, 3 × 10⁻⁶ M) attenuated phenylephrine-induced contraction in the present study. In addition, prazosin completely abolished fentanyl-induced attenuation of contractile response induced by phenylephrine. These results suggest that fentanyl attenuates the phenylephrine dose-response curve by inhibiting α1-adrenoceptor-mediated contraction of rat aortic smooth muscle. The CR which was calculated as the ratio of the ED₅₀ for phenylephrine in the presence or absence of fentanyl (10⁻⁶ M) was 2.52 ± 0.52, suggesting that the dose of phenylephrine required for the same magnitude of phenylephrine-induced contraction in the presence of fentanyl (10⁻⁶ M) is about 2.5 times higher than that in the absence of fentanyl. Fentanyl (100 ng/mL)
induces a small, but statistically significant attenuation of the phenylephrine concentration-response curve in isolated endothelium-intact canine coronary arteries.\(^8\) However, the present study showed that fentanyl at a concentration of 3 \( \times 10^{-7} \) M, which corresponds approximately to the plasma concentration (100 ng/mL) occurring in patients anesthetized with fentanyl for major surgery, had no effect on phenylephrine-induced contraction.\(^1\) The discrepancy in the results of the two studies may be ascribed to the difference in the vessel selected (endothelium-intact canine coronary artery versus endothelium-denuded rat aorta).

The estimated affinity of 5-MU for the \( \alpha_{1D} \)-adrenoceptor is approximately 10 times greater than that for the \( \alpha_{1A} \)-adrenoceptor and 100 times greater than that for the \( \alpha_{1B} \)-adrenoceptor.\(^5,10\) In the present \textit{in vitro} study, the affinity of 5-MU estimated in the rat aorta (p}\(\text{A}_2 \) = 7.71 ± 0.15) was close to the value expected for an interaction with the \( \alpha_{1D} \)-adrenoceptor (7.80 ± 0.09, 7.91 ± 0.07) rather than the \( \alpha_{1A} \)-adrenoceptor (8.50 ± 0.09, 8.68 ± 0.09) or \( \alpha_{1B} \)-adrenoceptor (6.80 ± 0.13, 6.76 ± 0.17).\(^5,10\) BMY 7378 is a selective \( \alpha_{1D} \)-adrenoceptor antagonist, whose selectivity for \( \alpha_{1D} \)-adrenoceptor is 100 times greater than that for the \( \alpha_{1A} \) or \( \alpha_{1B} \)-adrenoceptor.\(^5,10\) In this study, the estimated affinity of BMY 7378 was 8.99 ± 0.24, which is close to p}\(\text{K}_i \) values for the human recombinant \( \alpha_{1D} \)-adrenoceptor expressed in rat-1 fibroblast (9.39 ± 0.05) and the rat aorta (8.88 ± 0.10), demonstrating predominance of the \( \alpha_{1D} \)-adrenoceptor subtype.\(^5,10\) These results suggest that phenylephrine-induced contraction in rat aortic smooth muscle is primarily mediated by the \( \alpha_{1D} \)-adrenoceptor. The agreement between agonist potency and affinity for the \( \alpha_{1D} \)-adrenoceptor binding site shows that the \( \alpha_{1D} \)-adrenoceptor is responsible for mediating contraction of the rat aorta.\(^5,10\) The phenylephrine-induced contraction of the rat thoracic aorta is mainly mediated by the \( \alpha_{1D} \)-adrenoceptor.\(^5,9,20,21\) Consistent with previous studies,\(^9,19,21\) the present results suggest that the \( \alpha_{1D} \)-adrenoceptor is functionally important in mediating the phenylephrine-induced contraction of the rat aorta. Fentanyl (10\(^{-4} \) M) attenuated phenylephrine-induced contraction in rings when pretreated with 10\(^{-9} \) M 5-MU, but it did not significantly alter phenylephrine-induced contraction in rings pretreated with 3 \( \times 10^{-6} \) M BMY 7378. Together with the present results suggesting that the \( \alpha_{1D} \)-adrenoceptor is mainly involved in phenylephrine-induced contraction, these results suggest that fentanyl attenuates phenylephrine-induced contraction by inhibiting \( \alpha_{1D} \)-adrenoceptor-mediated contraction in the rat aorta. However, to lessen overestimation that may occur from concentration of 5-methylurapidil (10\(^{-4} \) M) and BMY 7378 (3 \( \times 10^{-9} \) M) adopted from previously reported p}\(\text{A}_2 \) values, competitive binding studies with radioisotope-tagged drugs are needed to examine the direct effect of fentanyl on \( \alpha_{1D} \)-adrenoceptor subtypes (\( \alpha_{1A} \) and \( \alpha_{1D} \)).\(^2\) In a radioligand binding study involving 20-min incubation at 37°C, the \( \alpha_{1D} \)-adrenoceptor was preferentially (89 to 98%) inactivated by the irreversible \( \alpha_{1D} \)-adrenoceptor antagonist (10\(^{-4} \) M CEC), followed by \( \alpha_{1A} \)-adrenoceptor at 75 to 86% and \( \alpha_{1D} \)-adrenoceptor at 11 to 18%.\(^22\) Rat aortic rings exposed to CEC (5 \( \times 10^{-6} \) M) show 20% reduction in phenylephrine-induced contraction.\(^23\) However, inhibition of contraction by pretreatment with 10\(^{-4} \) M CEC (20 min) was 72.9 ± 2.3% in this \textit{in vitro} study. This different effect of CEC on phenylephrine-induced contraction may be ascribed to the difference in the concentration of CEC, incubation period and washing method with fresh Krebs solution. CEC has been used extensively as a tool to discriminate \( \alpha_{1D} \)-adrenoceptor (CEC-insensitive) from \( \alpha_{1A} \)- and \( \alpha_{1D} \)-adrenoceptors (CEC-sensitive).\(^3\) Pretreatment of rat aorta with CEC (3 \( \times 10^{-6} \) M) showed 83.9% reduction of phenylephrine-induced contraction, which suggests that \( \alpha_{1D} \)-adrenoceptor subtype of the rat aorta is CEC-sensitive subtype (\( \alpha_{1D} \)- and \( \alpha_{1D} \)-adrenoceptors).\(^24\) Based on the findings of current and previous studies, CEC-sensitive \( \alpha_{1D} \)-adrenoceptor appears to be involved in the phenylephrine-induced contraction of the rat aorta.\(^8,24\) Interestingly, \( \alpha_{1D} \)-adrenoceptors seem to be regulated by crosstalk between G-protein-coupled receptors and subsequent signaling cascades.\(^25\) Further investigation is needed in order to determine the effect of fentanyl on G-protein, phospholipase C, the coupling processes, inositol 1,4,5-trisphosphate and diacylglycerol, since all these factors are involved in the cellular signal transduction pathway for \( \alpha_{1D} \)-adrenoceptor-mediated phenylephrine-induced contraction.

Fentanyl (2.97 \( \times 10^{-4} \) M) attenuates the nitric oxide-mediated relaxation induced by acetylcholine,\(^26\) and produces hypotension by inhibiting central sympathetic outflow in intact dogs anesthetized with enflurane.\(^27\) Previous studies have shown that fentanyl has no effect on myocardial contractility at a clinical dose and increases myocardial contractile force at supraclinical doses.\(^28,29\) According to the findings described above, the net hemodynamic effect of fentanyl \textit{in vivo} is a composite of the effect of fentanyl on blood vessel, central sympathetic activity and the heart.\(^26,29\) Any clinical implications of fentanyl on regional hemodynamics must be tempered by the fact that a large conduit artery, the aorta, was used in this \textit{in vitro} experiment, whereas the resistance vessels with the arterioles of a diameter of 100-300 µm control most organ blood flow.\(^29\) Even with these limitations, since 3 \( \times 10^{-7} \) M fentanyl (plasma fentanyl concentration 100 ìg/mL) did not alter phenylephrine-induced contraction, the indirect mechanism for vasodilation, which is mediated by decreased central sympathetic outflow induced by fentanyl, might be involved in the hypotension observed in the previous \textit{in vivo} studies.\(^1,2,19\)

Fentanyl significantly attenuated phenylephrine-induced contraction at concentrations of 10\(^{-4} \) and 3 \( \times 10^{-6} \) M, which
are higher than clinically relevant concentration (9.52 × 10^4 M). However, the rapid redistribution of fentanyl (octanol:water partition coefficient = 813) to lipid-rich tissue may create a discrepancy between the serum concentration and actual tissue concentration. Because cerebrospinal fluid contains very little protein in comparison to plasma, the average concentration of active fentanyl in cerebrospinal fluid is approximately 46% of the total plasma fentanyl concentration, which is more than twice the free fraction of plasma fentanyl. Small changes in the amount or binding capacity of proteins in certain pathologic conditions (example: liver disease, hemodilution, hypoproteinemia) could result in an increase in the free fraction of fentanyl. Taking the above findings into consideration, the 10^6 M concentration of fentanyl required for an inhibitory effect on phenylephrine-induced contraction might be the concentration encountered in clinical settings.

In conclusion, the present results suggest that fentanyl at supraclinical dose (10^6 M) attenuates phenylephrine-induced contraction of rat aortic smooth muscle by inhibiting the pathway involved in the α₁-adrenoceptor-mediated contraction. In addition, the α₁-adrenoceptor is functionally important in mediating phenylephrine-induced contraction of isolated rat aorta.

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