Letter to the Editor

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Antioxidant effects and mechanism of thiopental and propofol on the rabbit abdominal aortic endothelial dependent vasorelaxation against reactive oxygen species

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Reactive oxygen species (ROS), which are also generated in a normal condition in certain quantities, are generated in large quantities by ischemia or by oxygen resupply at the time of reperfusion and not reduced by the normal antioxidant systems of the body, eventually causing reperfusion injury in tissues [1].

In this study, we investigated whether thiopental and propofol, which are intravenous anesthetics, decrease endothelium injury by ROS and evaluated the mechanism for the decrease by causing endothelium-dependent relaxation of rabbit abdominal aortas.

All the experiments in this study were done after obtaining the approval of the Institutional Animal Care and Use Committee. Twenty four male New Zealand white rabbits (KOATECH, Pyeongtaek, Korea) weighing 2.0–2.5 kg were anesthetized with 3–5 vol% sevoflurane and 100% oxygen 4 L/min. Heparin 600 IU/kg was intravenously injected through the auricular marginal vein. Ten minutes after the heparin injection, the rabbit carotid artery was sectioned for exsanguinations, and the infra renal abdominal aorta was obtained.

ROS was generated by performing electrolysis (EL) of a K-H solution in an experimental bath. Two circular Platinum wire electrodes (7 mm) were positioned at the lower part of the experimental bath. Hemangioendothelial injury by ROS was induced by exposure to 15 mA DC constant current for 35 seconds (EL+) [2,3].

Thiopental and propofol, intravenous anesthetics, were put into the experimental bath at concentrations of 10^{-5} M, 3×10^{-5} M, 10^{-4} M, and 3×10^{-4} M and at concentrations of 10^{-4} M, 3×10^{-4} M, 10^{-3} M, and 3×10^{-3} M, respectively. After 15 minutes of pretreatment, EL+ was performed for 35 seconds. The used K-H solution was replaced with new K-H solution. After contracting the abdominal aorta by putting in NE, ACh at concentrations of 3×10^{-8} M, 10^{-7} M, 3×10^{-7} M, and 10^{-6} M was continuously added to the bath to relax the annular slices.

Cu/Zn superoxide dismutase (SOD) and catalase, which are important antioxidative enzymes, were pretreated with 0.8 mM diethyldithiocarbamate (DETCA) [4], a SOD inhibitor, for 30 minutes and with 50 mM 3-amino-1,2,4-triazole (3AT) [5], a catalase inhibitor, for 60 minutes.

While pretreating with DETCA and 3AT for 30 and 60 minutes in the experimental bath, respectively, thiopental (3×10^{-4} M) or propofol (3×10^{-3} M) was, respectively, added to the experimental bath 15 minutes before the completion of the pretreatment. After 15 minutes, EL was performed to generate ROS, and then the K-H solution was replaced with a new K-H solution. The annular slices were contracted and relaxed by adding NE and Ach to the bath.

All the data were expressed as the “Mean ± Standard Error” and the degree of ACh relaxation, calculated in percentage, was used as the control value.

The comparison of the results between the pretreated groups with respect to the thiopental and propofol concentrations was done by a one-way ANOVA and Dunnett test was done for a post-hoc test. An unpaired t-test was done to compare the aortic

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tension between the DETCA or 3AT pretreated groups and non-pretreated group. Values having a P value less than 0.05 were considered as significant.

In the thiopental 10^{-5} M, 3 × 10^{-5} M, 10^{-4} M, and 3 × 10^{-4} M pretreated groups, the relaxation reaction of vascular endothelium by ROS was proportional to the concentration. The rate of relaxation by 10^{-6} M ACh was −2.7 ± 0.9, −13.3 ± 2.5, −76.6 ± 1.5, and −85.6 ± 1.2%, respectively. A comparison of the thiopental 10^{-5} M group with the thiopental 3 × 10^{-5} M, 10^{-4} M, and 3 × 10^{-4} M groups showed that the relaxation rate of the annular slices was significantly higher in the thiopental 3 × 10^{-5} M, 10^{-4} M, and 3 × 10^{-4} M groups (P < 0.001). Similar to the thiopental pretreated groups, the propofol 10^{-4} M (n = 15), 3 × 10^{-4} M (n = 15), 10^{-3} M (n = 15), and 3 × 10^{-3} M (n = 15) groups showed a rate of relaxation by 10^{-6} M ACh of −4.6 ± −1.5, −19.1 ± 4.2, −61.6 ± 3.3, and −83.1 ± 1.7%, respectively. A comparison of the propofol 10^{-4} M group with the propofol 3 × 10^{-4} M, 10^{-3} M, and 3 × 10^{-3} M groups showed that the relaxation rate of the annular slices was significantly higher in the 3 × 10^{-4} M, 10^{-3} M, and 3 × 10^{-3} M groups (P < 0.001).

The annular slices relaxation rate of the DETCA + thiopental (3 × 10^{-4} M, n = 13, EL +) group after ROS exposure was −65.8 ± 2.9% which was significantly lower than the control value (EL-) −85.6 ± 1.2% for the thiopental 3 × 10^{-4} M group (P < 0.001). However, the annular slices relaxation rate of the 3AT + thiopental (3 × 10^{-3} M, EL +) group was −87.5 ± 1.3% which was not significantly different from the control value −86.6 ± 1.4% as well as the value of the thiopental 3 × 10^{-4} M group. The annular slices relaxation rate of DETCA + propofol (3 × 10^{-3} M, n = 15, EL +) after ROX exposure by EL was −51.6 ± 2.3% which was significantly lower than the control value (EL-) −85.1 ± 0.6% as well as the value −85.5 ± 1.8% for the propofol 3 × 10^{-3} M group (P < 0.001) (Fig. 1A). However, the annular slices relaxation rate of the 3AT + propofol (3 × 10^{-3} M, EL +) group was −88.8 ± 0.8% which was not significantly different from the control value −83.1 ± 1.7% as well as the value of the propofol 3 × 10^{-3} M group (Fig. 1B).

Because a superoxide anion radical is generated by the EL+ of K-H solution, hydrogen peroxide is generated subsequently. Then, hydroxyl radicals are generated through the Harber Weiss and Fenton reactions. The decrease in the relaxation rate in both the thiopental and propofol groups pretreated with DETCA inhibiting SOD suggests that both thiopental and propofol have an effect similar to that of SOD. In both the thiopental and propofol groups pretreated with 3-AT, a catalase inhibitor, the enzyme eliminating hydrogen peroxide as ROS superoxide, which is the precursor of hydrogen peroxide, might have already been eliminated by the SOD-like effect, and thus, hydrogen peroxide might have not been generated. Therefore, the 3-AT pretreatment might be insignificant.

On the other hand, when hydrogen peroxide was put added to SH-SY5Y cells to cause cell injury following eight hours of propofol pretreatment, the effect of hydrogen peroxide was attenuated by the ERK pathway. According to the result, a long duration of propofol pretreatment may be required to prevent, through propofol, the injury caused by hydrogen peroxide.

Thiopental and propofol decreased the injury caused by ROS to the rabbit abdominal aorta endothelium. The mechanism for the antioxidant effect of thiopental and propofol did not show a similar effect to that of catalase, which is a hydrogen peroxide scavenger, but showed a superoxide anion scavenging effect.

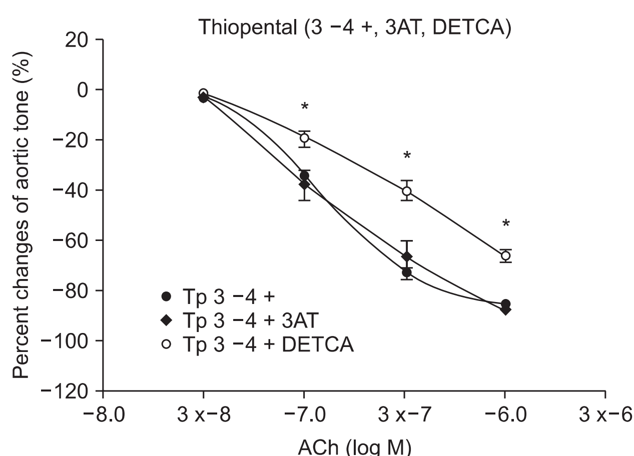

Fig. 1A. Concentration-response curves of acetylcholine (ACh)-induced endothelium-dependent relaxation after electrolysis in the in the presence of 3-amino-1,2,4-triazole (3AT), diethyldithiocarbamate (DETCA). Values are presented as mean ± SEM. *A P value of less than 0.001 significantly different from control group (Thiopental [Tp] 3 × 10^{-4}M).

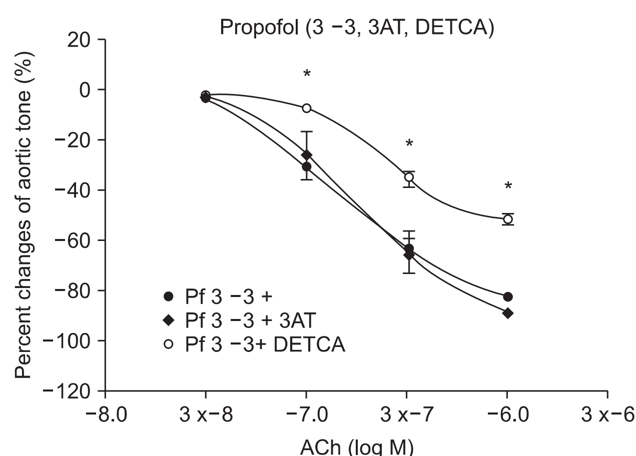

Fig. 1B. Relaxation effects of Propofol (Pf) (3 × 10^{-3}M) on exposure to the reactive oxygen species (ROS) in the presence or absence of 3-amino-1,2,4-triazole (3AT), diethyldithiocarbamate (DETCA). Values are expressed as mean ± SEM. *A P value of less than 0.001 significantly different from control group (Pf 3 −3 +).

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