

Effects of propofol on sympathetic neurotransmission in the isolated rat vas deferens

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This study was undertaken to determine the effect of propofol on sympathetic neurotransmission in the isolated rat vas deferens. Propofol (10⁻⁶ to 10⁻⁴M) reversibly reduced the contractile responses induced by exogenously applied noradrenaline (NA). The contractions evoked in the vas deferens by electrical field stimulation (EFS) did not change by propofol (10⁻⁶ to 10⁻⁴M), but at 70⁻⁴ propofol significantly increased contractu responses of EFS. Mephyramine, atropine, methysergid, indomethacin did not change the contractile responses of propofol to EFS, but this responses to EFS were inhibited by guanethedine. These results suggest that propofol (10⁻⁴ M) facilitates sympathetic neurotransmission in rat vas deferens by inhibiting neuronal uptake of the neurotransmitters in sympathetic nerve endings. On the other hand, effect of propofol (10⁻⁶ to 10⁻⁴M) to exogenously applied noradrenaline may be explained by modulation of the postsynaptic effects. [Turk J Med Res 1995, 13(4): 123-126]

Key Words: Propofol, Neurotransmission, Vas deferens, Rats

Propofol is a new intravenous anesthetic agent, chemically unrelated to barbiturate, steroids, imidazole or eurogenol agents. It is one of a series of alkyl phenols, found to have anesthetic properties in animals (1). The structure of propofol is 2,6 diisopropylphenol (ICI 35868). It is also known as Diprivan (trade name) and was previously known as diisopropofol (2,3). The ideal intravenous induction agent, possesses characteristics which include rapidity of onset and recovery, reliability of action (smooth onset without excitatory effects or respiratory distress, water solubility, lack of allergic responses and tissue toxicity, and lack of hemodynamic effects) (4).

Induction of anesthesia with iv propofol is often accompanied by hypotension, which has been ascribed to a decrease in either systemic vascular resistance (5) or cardiac output (6) or both (7,8). In an attempt to resolve the mechanism of the hypotensive activity (9), the agent was used in anesthetized dog preparation, in which all neurogenic cardiovascular reflexes had been abolished by bilateral vagotomy and common carotid ligatures, in combination with IV bretylium and propranolol. The study demonstrated

that blood propofol concentrations covering the clinical range in man cause direct vasodilatation in absence of sympathetic or vagal influences. It was concluded that anesthesia with propofol may be accompanied by decreased cardiac output secondary to reduction in preload by a direct venodilatory effect and this direct action is responsible for the clinically observed cardiovascular effect of the anesthetic.

The effects of propofol on the baroreceptor reflex shows that propofol does reset the baroreceptor reflex to allow slower heart rates, despite a decrease in arterial pressure (10,11). Propofol appears not to effect the baroreflex sensitivity (10,11). Studies of the direct effect of propofol on the sinoatrial node and atrioventricular conduction are incomplete in dogs and nonexistent in man (12).

Effect of propofol on sympathetic neurotransmission has not been studied in isolated rat vas deferens. This study was designed to examine effects of propofol on sympathetic neurotransmission and to compare it's effects with cocaine in rat vas deferens. We also aimed to investigate, the effects of propofol on the contractil response of the rat vas deferens to exogenously applied NA.

MATERIALS AND METHODS

Tissue Preparations: Albino rats weighing between 200-300 g were studied. The animals were killed by cervical dislocation, and the vasa deferentia were

Received: Jan. 18,1995

Accepted: June 11,1995

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quickly removed and placed in Krebs-bicarbonate buffer of the following composition (millimolar): NaCl, 112; KCl, 4.5; NaHCO₃, 25; NaHPO₄, 1.2; MgCl₂, 0.5; CaCl₂, 2.5; and glucose, 10. Vas deferens strips were attached to a glass rod and connected to the transducer and placed in an organ bath containing the Krebs-bicarbonate buffer. The solution was gassed with 95% O₂-5% CO₂ was maintained at 37°C. One gram of resting force was applied and allowed to equilibrate for 1.5h with washings at 15 min periods. Contractions were measured isometrically with Grass FT03 force-displacement transducers and recorded on a Grass polygraphy.

Responses to EFS in vitro: The isolated vas deferens strips were placed between bipolar platinum electrodes for applying EFS. Electrical stimuli, applied with Grass model S 88 stimulators, were at a supramaximal voltage (30V), a frequency of 0.05 Hz and stimulus duration of 0.5 msec. Swedin (13) found that electrical stimuli at less than 10 m sec durations stimulate only nerves in the preparation. This finding confirms that the electrically stimulated contraction was eliminated by tetrodotoxin (100 nM), suggesting that the contractile process was initiated by a neural event (14). Following this, concentration-response curves were obtained by cumulative increasing concentrations of propofol. Then, mephryamine, atropine, methysergid, indomethacin were added and 30 min later a new concentration-response curve to propofol was reobtained. In addition, the contractions of EFS were reobtained in the presence of 10⁻⁵ M cocaine.

Following drugs were used: Noradrenaline bitartrate (Sigma), propofol (ICI), cocaine hydrochloride (Geigy), guanethidine (Ciba), mephryamine hydrochloride (Sigma), atropine sulphate (Sigma), methysergid hydrochloride (Sigma), indomethacin hydrochloride (Sigma).

Responses to Exogenously Applied NA: Following equilibration period, a full concentration-response curve was obtained by stepwise increasing concentrations of NA. Each concentration was applied for 30s and then washed out thoroughly before the next higher concentration was added. There were 5 min intervals between successive concentrations of NA. Peak tension development after each concentration was used as the response in the construction of the concentration-response curve. This procedure was repeated in 30 min intervals until two successive curves were obtained in which the responses to successive addition of the agonist were almost identical in height. Then another 1.5h equilibration period ensued. During the last 5 min of this period, propofol was added to the organ bath and remained in the bathing solution throughout the construction of the concentration-response curves.

Statistical analysis: The mean values and their standard error (SE) were computed and subjected to statistical analysis for a significance of p<0.05 level using the student's t test for paired observations.

RESULTS

None of the propofol concentrations used (from 10⁻⁶ to 3.10⁻⁶ M) produced any change in the contractile response of the isolated vas deferens.

After incubation of the preparation with propofol (10⁻⁵ to 1CT⁻⁵ M) the contractile responses to all doses of NA were significantly decreased (Figure 1,2). The effects of propofol were rapidly reversed by replacing the media with drug-free Krebs-solution.

The effects of propofol (10⁻⁶ to 10⁻⁴ M) on the response of the vas deferens to EFS were studied in fourteen experiments. As illustrated in Figure 3a, the contractil response was significantly increased by concentrations 10⁻⁴ to 3.10⁻⁴ M of propofol used. When the drug was washed out, normal responses to EFS gradually reappeared.

Cocaine (10⁻⁵ M) significantly increased contractions of vas deferens to EFS (Figure 3b, 4). This responses to EFS were inhibited by guanethidine, but this responses of propofol were not prevented by mephryamine (10⁻⁵ M), atropine (10⁻⁶ M), methysergid (10⁻⁵ M), indomethacin (10⁻⁶ M).

DISCUSSION

Propofol (2,6-diisopropylphenol, ICI 35868) is rapidly acting iv anesthetic (1). Propofol induces a sustained blood pressure fall with transient reduction of cardiac output and systemic vascular resistance, at constant heart rate and preload (15). The mechanism of systemic hypotension may be due to systemic vasodilator and/or myocardial depression. The more pronounced decrease of systolic than diastolic blood pressure allows an analysis of the determinants of systolic blood pressure. Among these systemic arterial compliance seems most important as stroke volume and heart rate did not found to change (16).

The result of the present study shown that at 10⁻⁵ to 10⁻⁴ M propofol decreased contractile responses of

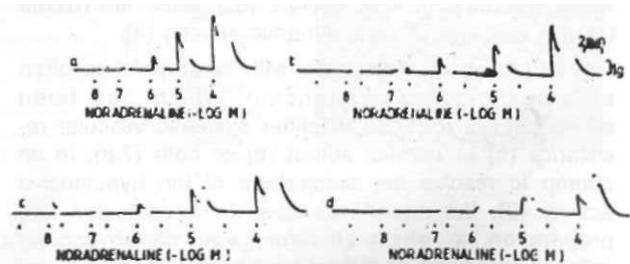


Figure 1. Effect of propofol on the contractile responses elicited in the rat vas deferens to exogenously applied noradrenaline.

1a. Control responses to exogenously applied noradrenaline.

1b. After incubation of the preparation with propofol (10⁻⁵ M), the contractile responses to noradrenaline.

1c. After incubation of the preparation with propofol (10⁻⁶ M), the contractile responses to noradrenaline.

1d. After incubation of the preparation with propofol (10⁻⁴ M), the contractil responses to noradrenaline.

the exogenously applied NA in isolated rat vas deferens, but at 10^{-3} - 10^{-4} M increased contractile responses of EFS.

In this study, both cocaine (10^{-6} M) and propofol (10^{-6} - $3 \cdot 10^{-6}$ M) significantly increased contractions of vas deferens to EFS. Although these responses of propofol to EFS were not changed by mephramine, atropine, methysergid and indomethacin, this effect of propofol was inhibited by guanethidine.

It has been proposed that nerve endings release NA in the isolated vas deferens of the rat (17), and

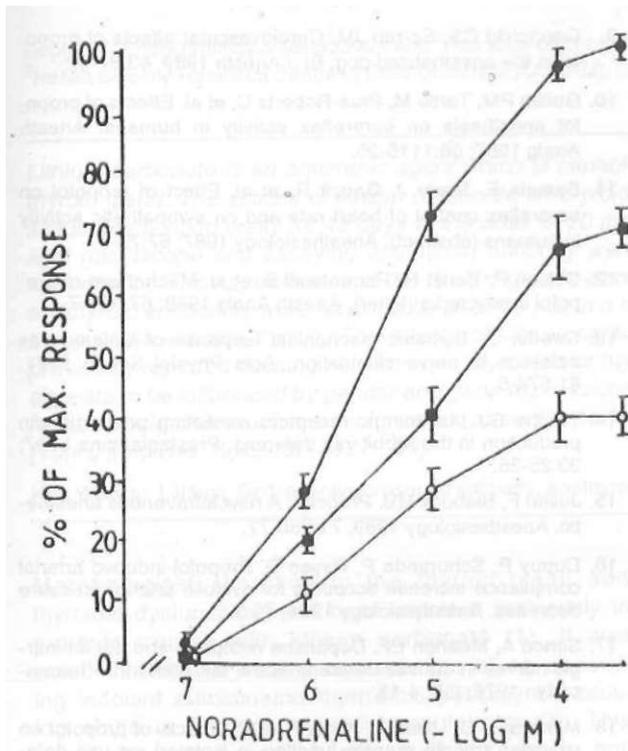


Figure 2. Effect of propofol on the concentration-response curves to exogenously applied noradrenaline in the rat vas deferens. Each point represents the mean \pm SE (n=14). Control responses to noradrenaline (\bullet), in presence of 10^{-5} M (\blacksquare), 10^{-6} M (\circ) propofol, responses to noradrenaline.

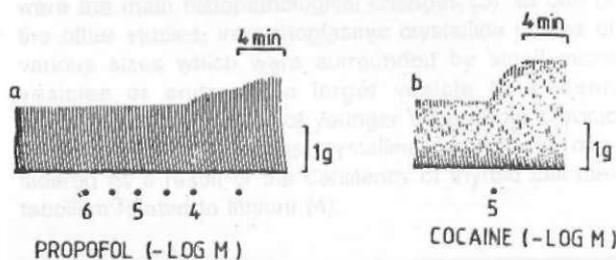


Figure 3. a. Effect of cumulative concentration of propofol on the contractile responses of the rat vas deferens elicited by electrical field stimulation (EFS). b. Effect of cocaine (10^{-6} M) on the contractile responses of the rat vas deferens elicited by electrical field stimulation (EFS).

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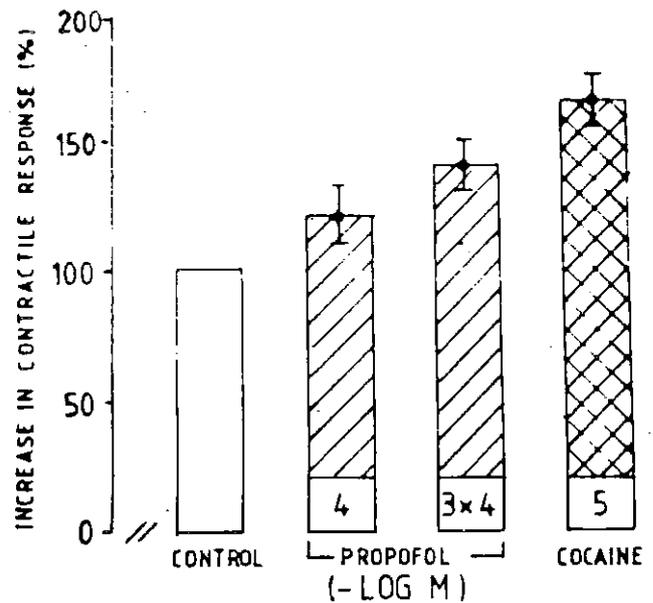


Figure 4. Effect of propofol and cocaine on the increase of contractility of isolated rat vas deferens strips evoked by EFS, significantly different from control values. Bars indicate mean \pm SE (n=14).

propofol depressed the responses to exogenously applied NA, but increased the responses by EFS. These findings suggest that propofol has both presynaptic and postsynaptic effects. Propofol-induced increase in adrenergic response to field stimulation in rat vas deferens may result from the inhibition of neuronal uptake of NA. When neuronal uptake mechanisms are inhibited with propofol, the potentiation of the response to noradrenaline might be expected to be amplified. Blockade of uptake mechanism may also be associated with overflow of the released sympathetic transmitter in the systemic circulation. Although, an effect of propofol on sympathetic neurotransmission has not been reported elsewhere, the effects of propofol on smooth muscle were previously observed in our laboratory (18). In this study we observed a relaxant effect of propofol in rat aorta which had been contracted by submaximal concentrations of phenylephrine. This study has confirmed that propofol in concentrations of 10^{-6} - 10^{-4} M, causes the relaxation of rat aortas (18). Similarly, Bentley et al (19) observed a relaxant effect of propofol in the rat aorta. Propofol caused significantly decreased responses to exogenously applied NA on vas deferens. If it had no relaxant effects of propofol on vas deferens smooth muscle, at these doses, perhaps, increased responses to EFS would occur highly.

In conclusion, data from the present study demonstrate that propofol increased EFS responses, which were caused by the release of naturally occurring neurohumoral transmitter in the rat vas deferens. Thus, this effect of propofol may be due to inhibition of neuronal uptake of NA (cocaine-like effect).

PROPOFOL'ÜN İZOLE RAT VAS DEFERENSİNDE SEMPATİK NÖROTRANSMİSYON ÜZERİNE ETKİLERİ

Bu çalışma izole rat vas deferensinde sempatik nörotransmisyon üzerine propofol'ün etkisini belirlemek için yapılmıştır. Propofol (1(T^s ile W^M), dışardan uygulanan noradrenaline (NA) neden olduğu kontraktıl cevapları reversible olarak azaltmaktadır. Elektriki alan uyarımı (EFS) ile başlatılan vas deferensdeki kontraksiyonlar propofol (10⁻⁵-10⁻³) ile değişmemektedir, ancak 10 M konsantrasyonundan propofol EFS'nin kontraktıl cevabını önemli ölçüde anırmaktadır. Mephyramine, atropine, methysergid, indomethacin EFS'ye propofol'ün kontraktıl cevaplarını değiştirmemektedir, ancak EFS'ye olan bu cevap guanethidine tarafından inhibe olmaktadır. Bu sonuçlar, propofol'ün (W^M) rat vas deferens'inde sempatik sinir uçlarında nörotrammittelerinin hümorale geri alımını inhibe ederek sempatik nörotransmisyonu kolaylaştırdığına işaret etmektedir. Diğer taraftan, dışarıdan uygulanan noradrenaline propofol (10⁻⁶-10⁻⁵ M) etkisi postsinaptik etkilerin modülasyonu ile açıklanabilir. [Turk J Med Res 1995, 13(4):123-126]

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