British Journal of Pharmacology (1998) 125, 120–126
http://www.stockton-press.co.uk/bjp

Differential effect of propofol on sympathetic neurotransmission in isolated human omental arteries and veins

[1,2]Susanna M. Wallerstedt & [1]Mikael Bodelsson

[1]Department of Anaesthesia and Intensive Care, University Hospital, S-221 85 Lund, Sweden

1 The present study was undertaken to elucidate the effect of propofol on sympathetic neurotransmission in isolated human omental vessels.

2 Segments of both arteries and veins were exposed to 0, 10^{-7}, 10^{-6}, 10^{-5} or 10^{-4} M propofol, and studied *in vitro* to determine effects on: (i) isometric tension after electrical field stimulation (EFS) or after exogenous administration of noradrenaline (NA); (ii) EFS-stimulated release of [^{3}H]-NA from vessel segments preincubated with [^{3}H]-NA; (iii) uptake of [^{3}H]-NA.

3 Propofol at 10^{-6} M enhanced EFS-induced contraction in artery segments, 10^{-7} and 10^{-5} M had no effect, and 10^{-4} M propofol depressed EFS-induced contraction in both artery and vein segments.

4 Propofol did not affect the response to exogenous NA in artery and vein segments.

5 EFS-stimulated release of [^{3}H]-NA was depressed by 10^{-5} and 10^{-4} M propofol in artery segments, and by 10^{-4} M in vein segments.

6 Uptake of [^{3}H]-NA was depressed by 10^{-6}–10^{-4} M propofol in artery but not in vein segments.

7 The results suggest that sympathetic neurotransmission is enhanced at clinical concentrations (10^{-6} M) of propofol in human omental arteries, but not veins. This may be due to an increased availability of NA in the neuromuscular junction resulting from a reduced presynaptic reuptake. Propofol at probably supraclinical concentrations (10^{-5}–10^{-4} M) impairs the sympathetic neurotransmission in both human omental arteries and veins, probably due to an inhibitory effect on the NA release from the sympathetic nerves.

Keywords: Anaesthetic; intravenous; propofol; omental artery; human; sympathetic nervous system: noradrenaline; omental vein

Introduction

The intravenous anaesthetic propofol reduces the arterial blood pressure (Grounds *et al*., 1985; Carmichael *et al*., 1993; Saarnivaara *et al*., 1993). Three possible underlying cardiovascular changes have been shown: a depressant effect on the myocardium (Grounds *et al*., 1985; Mulier *et al*., 1991), a decrease in systemic vascular resistance (SVR) (Boer *et al*., 1988; Claeys *et al*., 1988; Baraka *et al*., 1991; Boer *et al*., 1991; Price *et al*., 1992), and an increase in the venous capacitance (Robinson *et al*., 1994). One mechanism for the changes in SVR and venous capacitance may be a local effect on the blood vessel wall (Nakamura *et al*., 1992). Thus, propofol has been shown to alter the availability of free cytosolic calcium in vascular smooth muscle (Bentley *et al*., 1989; Bunting *et al*., 1989; Chang & Davis, 1993; Introna *et al*., 1993; Yamanoue *et al*., 1994; Kamitani *et al*., 1995; Wallerstedt & Bodelsson, 1997a) and also to affect the function of the endothelium (Park *et al*., 1992; Petros *et al*., 1993; Mimaroglu *et al*., 1994; Gacar *et al*., 1995; Park *et al*., 1995).

Sympathetic nerve activity contributes to blood pressure regulation in part by its influence on vascular smooth muscle. In fact, another possible mechanism for the changes in SVR and capacitance during propofol anaesthesia seems to be a central inhibition of the sympathetic outflow (Robinson *et al*., 1997; Sellgren *et al*., 1990). However, an effective sympathetic neuromuscular coupling in the blood vessel wall is mandatory for the central regulation and is another putative site for the cardiovascular actions of anaesthetics. Several studies have demonstrated an impairment of vascular sympathetic neurotransmission in the presence of anaesthetics. For example, vascular smooth muscle contraction induced by electrical field stimulation (EFS) *in vitro* is generally more inhibited by volatile anaesthetics than contraction induced by exogenous noradrenaline (NA) (Muldoon *et al*., 1975; Kobayashi *et al*., 1990; Stadnicka *et al*., 1993). This indicates that volatile anaesthetics may be able to decrease the prejunctional release of the transmitter (Roizen *et al*., 1976; Lunn & Rorie, 1984; Kobayashi *et al*., 1990). The net effect of anaesthetics on the sympathetic neurotransmission will also be dependent on effects of the anaesthetics on the smooth muscle response as well as effects on the removal of the transmitters from the neuromuscular junction.

The aim of the present study was to elucidate the effect of propofol on the sympathetic neurotransmission in human omental arteries and veins focusing on (i) smooth muscle contraction in response to EFS and exogenous NA, (ii) EFS-induced release of transmitter from the perivascular nerves and (iii) effects on the neuronal transmitter reuptake.

Methods

The study was approved by the Ethical Committee of the University of Lund. Macroscopically normal segments of human omental arteries and veins were obtained, from 15 male and 13 female patients aged 30–92 years (median 69.5) undergoing gastrectomy, small or large bowel resection, liver resection or pancreatectomy. Patients with endocrine tumors, abdominal infections and previous radiotherapy were excluded. The outer diameter of the vessels were 0.5–1 mm and

[2]Author for correspondence.

1–1.5 mm for arteries and veins respectively. The experiments were carried out the same day as the vessels were removed from the patients. The vessels were dissected free from fat and connective tissue.

Measurement of changes in isometric tension

The vessels were cut into 2–4 mm long ring segments. The segments were placed in 2 ml tissue baths on two L-shaped hooks, one of which was attached to a Grass FTO3C force-displacement transducer for isometric measurement of tension. The vessel tension was recorded on a Grass polygraph model 7b (Grass Medical Instruments, Quincy, Mass., U.S.A.). The baths were thermostatically kept at 37°C and contained lipid Krebs-Ringer solution (lipid-KRS, composition (mM): Na^+ 143, K^+ 4.6, Cl^- 126.4, Ca^{2+} 2.5, HCO_3^- 25.0, Mg^{2+} 0.79, SO_4^{2-} 0.79, $H_2PO_4^-$ 1.2, Glucose 5.5, EDTA 0.024 and 0.18% Intralipid® 10% i.e. (g/l): soy bean oil 0.178, egg phospholipid 0.021, glycerol USP 0.04). The solution was continuously aerated with 88.5% O_2 and 11.5% CO_2. The gas flow was adjusted to give pH 7.4, PCO_2 5.0 kPa and PO_2 approximately 40 kPa. The lipid-KRS was changed at least every 30 min.

The use of lipid-KRS made it possible to keep a constant lipid concentration in the baths when propofol was added in concentrations achieved by dilution of Diprivan®. The highest concentration of propofol that was investigated was 10^{-4} M. This concentration was achieved by adding 20 μl of 10^{-2} M propofol to 2 ml tissue baths containing normal Krebs-Ringer solution (KRS). 10^{-2} M propofol was achieved by diluting Diprivan® 5.6 times. Consequently, the resulting dilution of Diprivan® is 5.6×100. In the experiments with propofol at concentrations $< 10^{-4}$ M, lipid-KRS was used, i.e. KRS with Intralipid® at a dilution of 1:560 (0.18%). Since the concentration of lipid was the same in all experiments, the only factor that varied was the concentration of propofol. Hence, differences in the response should be due to differences in the propofol concentration. Pilot experiments had shown that the contraction induced by 90 mM KCl was the same in KRS with and without Intralipid®.

The vessel segments were gradually stretched to a resting tension of 6 mN during an equilibration period of 60-90 min to obtain the optimal tension level (Wallerstedt & Bodelsson, 1997b). After the equilibration period, KCl (90 mM) was added to the baths repeatedly, each time followed by wash-out, until consistent contractions were elicited (two to three times).

Electrical field stimulation (EFS) Platinum electrodes were mounted on either side of each vessel segment with a 4 mm distance between the electrodes. The electrodes were connected to a custom-made square wave stimulator with adjustable voltage, current, frequency and duration of pulse. The resulting amplitude of the square wave was continuously measured with an oscilloscope (Tektronix, U.K. Ltd). 30-s pulse trains were used and a 5 min resting period was allowed between each stimulation. To find the optimal stimulation parameters, resulting in nerve but not smooth muscle stimulation, artery and vein segments were tested at different voltage levels and different pulse duration in the presence and absence of the neuronal blocker tetrodotoxin (TTX, 10^{-6} M). The optimal parameters, which resulted in less than 10% response in the TTX-treated artery segments and less than 5% response in the TTX-treated vein segments compared to the untreated segments, was 12 v, 0.1 ms for the artery segments and 8 V, 0.1 ms for the vein segments. The consecutive experiments were performed using these parameters. TTX-treated segments were always run in parallel and if the contractile response induced by EFS was greater than 10% (artery) and 5% (vein) the results were excluded.

Experimental protocols

The smooth muscle response of the vessel segments to EFS and exogenous NA was investigated. First, EFS was performed (see above) at frequencies of 1, 2, 4, 8, 16 and 32 Hz. The resulting vessel contraction was registered and the greatest contraction achieved for each segment was used as a neurogenic reference contraction. After a completed frequency response series, the lipid-KRS was changed and the endogenous NA stores were replenished by performing a concentration-response experiment with exogenous NA (Urabe *et al.*, 1991), by adding NA cumulatively in $_{10}$log units to achieve bath concentrations of 10^{-9}–10^{-4} M. The contraction was registered and the greatest contraction elicited was used as an exogenous NA reference contraction. After a completed concentration-response series the baths were washed several times until the tension returned to the baseline level tension. Then Diprivan® or Intralipid® 10% diluted in KRS to achieve propofol-concentrations of 0, 10^{-7}, 10^{-6}, 10^{-5} or 10^{-4} M in lipid-KRS was added to the baths (see above). After 10 min the bath content was changed and the same concentration of propofol or Intralipid® 10% was added again. The frequency-response experiments were performed as above. The EFS-induced contractions are expressed as % of the neurogenic reference response. Following wash-out propofol or Intralipid® 10% was added (0, 10^{-7}, 10^{-6}, 10^{-5} or 10^{-4} M, respectively) and 10 min later the bath content was changed and the same concentration of propofol or Intralipid® 10% was added again. Exogenous NA was added cumulatively as above. The resulting contractions are expressed as % of the exogenous NA reference contraction. The use of the reference contractions made it possible to correct for differences in contractility between the vessel segments owing to various length and nerve fibre density. 1–2 control vessel segments not exposed to propofol were always run in parallel. In the statistical analysis, the data generated from these control segments was compared to the data from the propofol-treated segments.

Measurement of release of [^{3}H]-NA

The device for studying the release of tritiated neurotransmitters has previously been described (Wikberg & Axelsson, 1980). Four artery or vein segments (approximately 1 cm in length) from each patient were preincubated (at 37°C, pH 7.4, PCO_2 5.0 kPa and PO_2 approximately 40 kPa) for 10 min in KRS followed by incubation with [^{3}H]-NA (10^{-7} M; radioactivity: 2.0535 TBq/mmol) for 40 min in the presence of normetanephrine (10^{-5} M) to block extraneuronal amine uptake (Burgen & Iversen, 1965). The vessel segments were rinsed four times over 50 min in lipid-KRS containing normetanephrine and the neuronal NA uptake blocker desipramine (6×10^{-7} M) (Byg *et al.*, 1994). Then the segments were mounted on perspex holders with platinum ring electrodes surrounding the preparation (Kannisto *et al.*, 1987). The holders were placed in vials containing 3 ml aerated lipid-KRS with normetanephrine and desipramine kept at 37°C and transferred to new vials containing the same medium every 2 min.

EFS was applied at 30-s pulse trains (0.5 ms, 30 V, 32 Hz) in three to four stimulation periods after 12, 24, 36 and 48 min. There was a resting period of 11.5 min between each

stimulation. Propofol (0, 10^{-6}, 10^{-5} or 10^{-4} M) or TTX (10^{-6} M) were added in one to two vials out of four, in six consecutive vials, so that the vessel segments were exposed to the drug or the solvent Intralipid® for 10 min prior to EFS and during EFS.

The experiments were concluded by determining the radioactivity in each vial in a liquid scintillation counter after addition of 10 ml Optiphase 3. The tissue specimens were blotted on a filter paper, weighed, hydrolyzed in 1 ml Optisolve for 120 min at 50°C, and 10 ml Optiphase 2 was added for determination of the remaining radioactivity of each vessel segment. The radioactivity in the vials is expressed as percent of the total radioactivity of the corresponding vessel segment at the actual time. The background radioactivity was estimated in vials with 10 ml Optiphase 3 added to 3 ml lipid-KRS and 10 ml Optiphase 2 added to 1 ml Optisolve respectively.

Measurement of uptake of [^{3}H]-NA

Artery and vein segments (0.5–1 cm in length) were mounted on steel wires (0.4 mm in cross section diameter) and placed in aerated lipid-KRS at 37°C for 10 min. They were then exposed to propofol (0, 10^{-7}, 10^{-6}, 10^{-5} or 10^{-4} M) or to desipramine (6×10^{-7} M) during a 15 min preincubation period in lipid-KRS with normetanephrine (10^{-5} M). Subsequently, they were transferred to new vials containing the same medium plus [^{3}H]-NA (10^{-7} M, 0.5 ml) for a 15 min incubation period. Consequently, in experiments with propofol and desipramine the drug was present throughout the preincubation and the incubation periods. Following the incubation, the vessel segments were placed in KRS at 4°C for 5 min to stop the uptake. Eventually the segments were blotted on a filter paper, weighed, hydrolyzed in 1 ml Optisolve for 120 min at 50°C, and 10 ml Optiphase 2 was added for determination of radioactivity in each segment. The background radioactivity was estimated as above.

Statistical analysis

The maximum response elicited by the agonist (E_{Am}) and the EC_{50} value were calculated. EC_{50} values are expressed as pD_2 values, which are defined as $-\log_{10}(EC_{50})$. In the experiments with release and uptake of [^{3}H]-NA, the background radioactivity was subtracted before analysis and presentation. When similar experiments were performed on more than one segment from the same patient, the mean for each patient was calculated before presentation and statistical analysis. The control values presented were always obtained from simultaneously run experiments on segments not treated with propofol. The number of individuals is indicated with '*n*'. Values are expressed as mean ± s.e.m. Student's paired *t*-test was used for statistical evaluation. For evaluation of EFS- and NA-induced contractions, the area under curve was compared (Matthews *et al*., 1990). A *P*-value less than 0.05 was considered statistically significant.

Materials

The following compounds were used: propofol (Diprivan®, Zeneca); L(−)-noradrenaline bitartrate (NA, RBI); Intralipid® 10% (Pharmacia Upjohn); tetrodotoxin (TTX, RBI); noradrenaline L-[ring-2,5,6-^{3}H] ([^{3}H]-NA, DuPont NEN); DL-normetanephrine (Sigma); desipramine (Sigma); Optiphase 2 and 3 (Wallac); Optisolve (Wallac). NA and [^{3}H]-NA were dissolved in KRS. The other drugs were dissolved in distilled water.

Results

The results are summarized in Table 1.

Changes in isometric tension due to EFS and NA

In the artery segments, the EFS-induced contractions were enhanced by 10^{-6} M propofol ($P=0.004$), unaffected by 10^{-7} and 10^{-5} M propofol ($P>0.05$) and depressed by 10^{-4} M propofol ($P<0.001$, Figure 1a). In the vein segments, the EFS-induced contractions were not affected by 10^{-7}–10^{-5} M propofol ($P>0.05$), but were depressed by 10^{-4} M propofol ($P=0.040$, Figure 1b). NA induced concentration-dependent contraction in both artery (E_{Am}: 69 ± 8, pD_2: 5.78 ± 0.15, $n=9$) and vein segments (E_{Am}: 108 ± 5, pD_2: 6.59 ± 0.22, $n=8$). The NA-induced contractions were not affected by 10^{-7}–10^{-4} M propofol in artery or vein segments ($P>0.05$, not shown).

Release of [^{3}H]-NA

TTX totally inhibited the release of [^{3}H]-NA by EFS in both artery ($n=3$) and vein ($n=3$) segments. In the artery segments, the release of [^{3}H]-NA was unaffected by 10^{-6} M propofol ($P>0.05$), but was inhibited by 10^{-5} ($P=0.038$) and 10^{-4} M propofol ($P=0.006$, Figure 2a). In the vein segments, the release of [^{3}H]-NA was unaffected by 10^{-6} and 10^{-5} M propofol ($P>0.05$), but was inhibited by 10^{-4} M propofol ($P=0.041$, Figure 2b).

Uptake of [^{3}H]-NA

In the artery segments, the uptake of [^{3}H]-NA was not affected by propofol at 10^{-7} M ($P>0.05$, $n=4$, not shown), but was reduced in the presence of 10^{-6}, 10^{-5} and 10^{-4} M propofol ($P=0.014$, 0.010 and 0.033, respectively). In the vein segments, propofol at the concentrations tested (10^{-6}–10^{-4} M) did not affect the uptake of [^{3}H]-NA ($P>0.05$). Desipramine reduced the uptake of [^{3}H]-NA in both artery and vein segments ($P=0.002$ and 0.003, respectively, Figure 3).

Table 1 Summary of the effects of propofol on electrical field stimulation-induced contractions (EFS), NA-induced contractions (exogenous NA), release and uptake of [^{3}H]-NA

	Contraction				*[^{3}H]-NA*			
	EFS		*Exogenous NA*		*Release*		*Uptake*	
Propofol	*a(9)*	*v(8)*	*a(9)*	*v(8)*	*a(6)*	*v(6)*	*a(6–8)*	*v(5–6)*
10^{-6} M	↑	0	0	0	0	0	↓	0
10^{-5} M	0	0	0	0	↓	0	↓	0
10^{-4} M	↓	↓	0	0	↓	↓	↓	0

a: artery segments; v: vein segments; numbers within brackets: number of individuals (n).

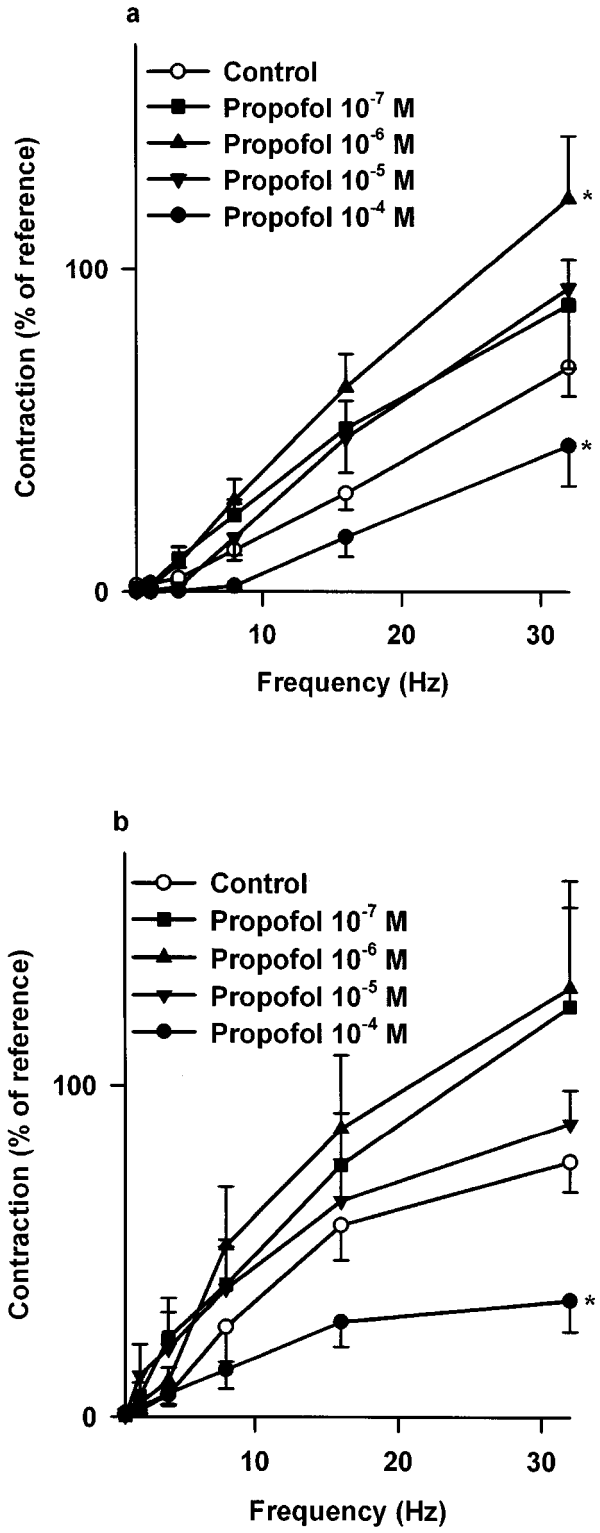

Figure 1 Frequency-response curves obtained by electrical field stimulation (EFS) of human omental artery (a) and vein (b) segments in the presence of 0, 10^{-7}, 10^{-6}, 10^{-5} and 10^{-4} M propofol. The reference contractions were (artery, mN): 3.4±1.3, 3.0±0.5, 0.8±0.2, 1.3±0.4 and 0.8±0.3, respectively, and (vein, mN): 7.2±2.1, 5.7±1.5, 4.7±2.0, 6.1±3.0 and 7.1±2.9, respectively. In the artery segments, 10^{-6} M propofol enhanced and 10^{-4} M propofol diminished the EFS-induced contractions compared to control. In the vein segments, 10^{-4} M propofol diminished the EFS-induced contractions. Student's *t*-test was used to compare area under curve, $^{*}P<0.05$ versus control. Values are mean±s.e.mean. Number of individuals tested (n) = 8-9.

Discussion

The magnitude of the vascular smooth muscle contraction induced by sympathetic nerve discharge is dependent on the balance between several factors. Firstly, the concentration of the transmitter (NA) in the neuromuscular junction is determined by the relation between the amounts of NA released and reuptaken by the nerves. Secondly, the contractile response of the smooth muscle cells to the resulting transmitter concentration is dependent on the effectiveness of the smooth muscle receptors and their coupling to the contractile machinery. The present study reveals concentration-dependent effects of propofol on EFS-induced smooth muscle contraction, which may be explained by the complex actions of the anaesthetic on transmitter release and transmitter reuptake.

In the artery segments, 10^{-6} M propofol enhanced the contractile effect of EFS. The present results suggest that

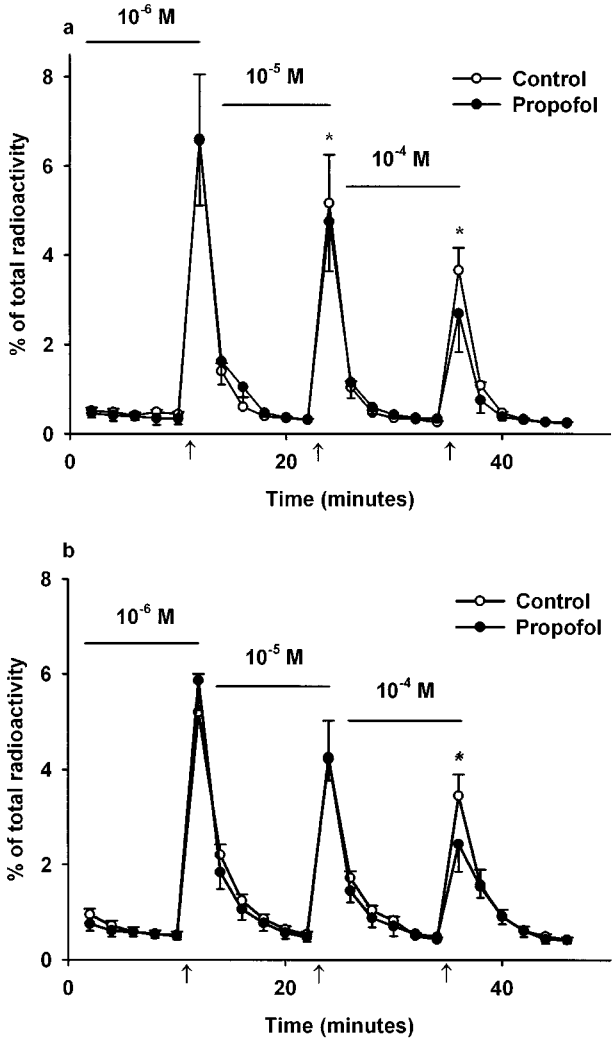

Figure 2 Release of tritium expressed as % of the total radioactivity in human omental artery (a) and vein (b) segments preincubated with [^{3}H]-NA. Electrical field stimulation (EFS) was applied at 12, 24 and 36 min (↑). Open symbols indicate control values and filled symbols indicate values in the presence of propofol at a concentration of 10^{-6} M (0-14 min), 10^{-5} M (14-26 min) and 10^{-4} M (26 - 38 min). In the artery segments, 10^{-5} and 10^{-4} M propofol reduced the stimulated release of tritium. In the vein segments, 10^{-4} M propofol reduced the stimulated release of tritium. Student's paired *t*-test was used, $^{*}P<0.05$. Values are mean±s.e.mean. Number of individuals tested (n) = 6.

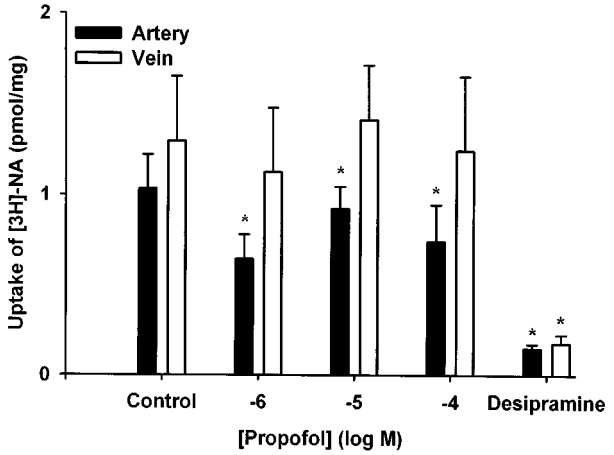

Figure 3 Uptake of [^{3}H]-NA expressed as pmol/mg tissue in human omental artery and vein segments incubated with [^{3}H]-NA in the absence (control) or presence of propofol (10^{-6}, 10^{-5}, 10^{-4} M) or in the presence of desipramine (6×10^{-7} M). 10^{-6} – 10^{-4} M propofol reduced the uptake in the artery segments. The uptake in vein segments was not affected by propofol at the concentrations tested. Desipramine markedly reduced the uptake of [^{3}H]-NA in both artery and vein segments. Student's paired *t*-test was used, $^*P<0.05$ versus control. Values are mean ± s.e.mean. Number of individuals tested (n) = 5-8.

neither increased smooth muscle contraction by NA nor facilitated neuronal release of NA can explain this, since propofol at this concentration affected neither the concentration-response curves of exogenously administered NA nor the release of [^{3}H]-NA. However, propofol at this concentration inhibited the uptake of [^{3}H]-NA indicating that the clearance of NA from the neuromuscular junctions during EFS may be impaired. These findings suggest that the enhancement of EFS-induced contraction in the artery at 10^{-6} M propofol may be due to an increased NA concentration in the neuromuscular junction. It cannot be excluded that additional mechanisms may be involved in the enhancement of the EFS-induced contraction by propofol at 10^{-6} M, i.e. effects on other transmitters such as neuropeptide Y and adenosine triphosphate (ATP) released from the perivascular nerves (Lundberg, 1996). We performed extensive pilot experiments in order to optimize the voltage and pulse duration used in the EFS experiments. Unfortunately, it was not possible to find stimulation parameters with less response in the presence of TTX than 10% for the arteries and 5% for the veins. We were therefore forced to accept this uncertainty in the data interpretation. There was a considerable variation between the different segments in the contraction induced by EFS, especially in the arteries. The variability could be due to differences in length and nerve fibre density of the segments used.

An increased level of smooth muscle tension at low concentrations of propofol has previously been shown in isolated canine coronary arteries (Introna *et al*., 1993). The enhancement of the EFS-induced contractions at 10^{-6} M propofol found in the present study could also be the result of a propofol-induced inhibition of dilating mechanisms – e.g. endothelial release of EDRF:s as in the rabbit mesenteric arteries (Kamitani *et al*., 1995). This seems unlikely since propofol has been reported to act endothelium-independently in human omental arteries and veins (Wallerstedt *et al*., 1998).

In the artery, propofol at 10^{-5} M did not alter the contractile effect of EFS. This may be explained by a simultaneous inhibition of both the presynaptic release and reuptake of NA by propofol, giving no net change in the NA concentration in the neuromuscular junction and consequently no change in the resulting contractile response induced by EFS.

The lipid solubility of propofol (5000 : 1; lipid : aqueous partitioning) (Park *et al*., 1992) and a high degree of plasma protein binding (98%) (Servin *et al*., 1988) are factors that contribute to the difficulty to extrapolate *in vitro* to *in vivo* concentrations. Park *et al*., (1992) have suggested that an *in vitro* concentration of propofol around 10^{-6} M may relevantly reflect the *in vivo* situation during anaesthesia with propofol.

Earlier findings *in vivo* in man (Sellgren *et al*., 1990) suggest that a depression of the sympathetic activity may contribute to the propofol-induced hypotension. In a recent study, Robinson *et al*., (1997) using forearm venous occlusion plethysmography, could not detect any vasodilation upon local infusion of propofol into the brachial artery. Furthermore, anaesthesia with propofol resulted in vasodilation, but only if the sympathetic transmission was intact. These results indicate that propofol in clinically relevant concentrations induces vasodilation in the forearm *via* inhibition of the sympathetic activity rather than a local effect on the blood vessels.

The present results suggest that propofol, at clinically relevant concentrations, enhances the vascular effects of sympathetic neuronal firing. This may be regarded as a contradiction to the findings of the study of Robinson *et al*., (1997). However, the results from that study suggest that the vasodilation induced by propofol is the result of an action on the central sympathetic outflow and/or on the peripheral sympathetic ganglia. The study by Sellgren *et al*., (1990)) suggest that there is a marked depression of the sympathetic activity in the postganglionic neurones at clinically relevant concentrations of propofol. Our finding of a modestly augmented sympathetic neuromuscular transmission may be overcome by a more profound depression of more proximal mechanisms. The net effect could then be a depression of the sympathetic activity, as observed by Robinson *et al*., (1997).

The present study thus supports the view that local effects on blood vessels may be less important than central effects to explain the hypotension associated with propofol anaesthesia. Propofol at concentrations around 10^{-6} M may instead promote the effects of the sympathetic discharge by inhibiting the prejunctional reuptake process, at least in arteries.

In both artery and vein, propofol at 10^{-4} M decreased the contractile response induced by EFS. This seems to be due to a presynaptic inhibition of the nerve terminals, since the stimulated release of [^{3}H]-NA was markedly reduced without any further uptake inhibition at this concentration. The concentration required to depress the sympathetic neuromuscular transmission in both artery and vein may be too high to be clinically relevant. This contrasts to the findings in the rat femoral artery, where the contractile response to EFS was inhibited at a lower, possibly clinically more relevant concentration of propofol (Biddle *et al*., 1995). An explanation for the discrepancy in the findings may be that propofol acts differently in various vascular beds and/or species.

The present results indicate that propofol may function as a peripheral neuronal NA uptake inhibitor. In the artery, the neuronal uptake inhibition was a concentration-dependent effect with a pIC_{50} of 6 – 7. The relative high potency suggests that the uptake inhibition could occur at clinical concentrations of propofol. In cultured bovine adrenal medulla cells, propofol at a somewhat higher concentration ($1-5\times10^{-5}$ M) inhibits imipramine-sensitive uptake of [^{3}H]-NA (Minami *et al*., 1996). On the other hand, in SH-SY5Y human

neuroblastoma cells, a cell line of probably noradrenergic origin, propofol (10^{-4} M) does not alter [^{3}H]-NA uptake (Cembala *et al*., 1994).

The considerable variation in the vascular sympathetic neuroeffector system (Bevan, 1979) may explain the differing actions of propofol on sympathetic neurotransmission in the arterial compared to the venous side of the circulation. In the arteries, clinically relevant concentrations of the anaesthetic are sufficient to affect both release and uptake of NA. In the veins, the uptake of NA was unaffected by propofol and the release only inhibited at supraclinical propofol concentrations. If the present results are applicable to a far wider array of vessels in the body, in the clinical situation, propofol primarily would affect the sympathetic neurotransmission in the arteries.

In conclusion, the effect of propofol on vascular sympathetic transmission is concentration-dependent with a facilitation in the artery at low concentrations and a depression in both artery and vein at high, possibly not clinically relevant, concentrations.

This study was supported by the Lund University Hospital Research Funds, the Anna Lisa and Sven-Eric Lundgren Foundation, the Swedish Society of Medicine, the Thelma Zoéga Foundation and the Stig and Ragna Gorthon Foundation.

References

BARAKA, A., DABBOUS, A., SIDDIK, S. & BIJJANI, A. (1991). Action of propofol on resistance and capacitance vessels during cardiopulmonary bypass. *Acta Anaesthesiol. Scand.,* **35,** 545–547.

BENTLEY, G.N., GENT, J.P. & GOODCHILD, C.S. (1989). Vascular effects of propofol: smooth muscle relaxation in isolated veins and arteries. *J. Pharm. Pharmacol.,* **41,** 797–798.

BEVAN, J.A. (1979). Some bases of differences in vascular response to sympathetic activity. *Circ. Res.,* **45,** 161–171.

BIDDLE, N.L., GELB, A.W. & HAMILTON, J.T. (1995). Propofol differently attenuates the responses to exogenous and endogenous norepinephrine in the isolated rat femoral artery in vitro. *Anesth. Analg.,* **80,** 793–799.

BOER, F., BOVILL, J.G., ROS, P. & VAN OMMEN, H. (1991). Effect of thiopentone, etomidate and propofol on systemic vascular resistance during cardiopulmonary bypass. *Br. J. Anaesth.,* **67,** 69–72.

BOER, F., ROS, P. & BOVILL, J.G. (1988). Propofol decreases systemic vascular resistance during cardiopulmonary bypass. *Br. J. Anaesth.,* **61,** 108.

BUNTING, P., RAMSAY, T.M. & PLEURY, B.J. (1989). An *in-vitro*, study of the interactions between intravenous induction agents and the calcium antagonists verapamil and nifedipine. *J. Pharm. Pharmacol.,* **41,** 840–843.

BURGEN, A.S.V. & IVERSEN, L.L. (1965). The inhibition of noradrenaline uptake by sympathomimetic amines in the rat isolated heart. *Br. J. Pharmacol.,* **25,** 34–49.

BYG, A.M., BUND, S., MULVANY, M.J. & AALKJAER, C. (1994). The effect of cocaine and desipramine on neuronal uptake of [^{3}H]-noradrenaline and sensitivity to noradrenaline of rat mesenteric resistance arteries. *Clin. Exp. Pharmacol. Physiol.,* **21,** 623–630.

CARMICHAEL, F.J., CRAWFORD, M.W., KHAYYAM, N. & SALDIVIA, V. (1993). Effect of propofol infusion on splanchnic hemodynamics and liver oxygen consumption in the rat. *Anesthesiology,* **79,** 1051–1060.

CEMBALA, T.M., FROST, C.L., ATCHESON, R., HIRST, R.A., SMART, D. & LAMBERT, D.G. (1994). Effects of propofol on cAMP and Ins(1,4,5)P3 formation and ^{3}H-noradrenaline uptake and release from SH-SY5y cells. *Biochem. Soc. Trans.,* **22,** 290.

CHANG, K.S.K. & DAVIS, R.F. (1993). Propofol produces endothelium-independent vasodilation and may act as a Ca^{2+} channel blocker. *Anesth. Analg.,* **76,** 24–32.

CLAEYS, M.A., GEPTS, E. & CAMU, F. (1988). Haemodynamic changes during anaesthesia induced and maintained with propofol. *Br. J. Anaesth.,* **60,** 3–9.

GACAR, N., GÖK, S., KALYONCU, N.I., ÖZEN, I., SOYKAN, N. & AKTÜRK, G. (1995). The effect of endothelium on the response to propofol on bovine coronary artery rings. *Acta Anaesthesiol. Scand.,* **39,** 1080–1083.

GROUNDS, R.M., TWIGLEY, A.J., CARLI, F., WHITWAM, J.G. & MORGAN, M. (1985). The haemodynamic effects of intravenous induction. *Anaesthesia,* **40,** 735–740.

INTRONA, R.P.S., PRUETT, J.K., YODLOWSKI, E.H. & GROVER, E. (1993). Direct effects of propofol (2,6-diisopropylphenol) on canine coronary artery ring tension. *Gen. Pharmacol.,* **24,** 497–502.

KAMITANI, K., YAMAZAKI, M., YUKITAKA, M., ITO, Y. & MOMOSE, Y. (1995). Effects of propofol on isolated rabbit mesenteric arteries and veins. *Br. J. Anaesth.,* **75,** 457–461.

KANNISTO, P., HÅKANSON, R., OWMAN, C., SCHMIDT, G. & WAHLESTEDT, C. (1987). GABA suppresses stimulation-induced release of (3H)-noradrenaline from sympathetic nerve fibres in bovine ovarian follicles. *J. Auton. Pharmacol.,* **7,** 339–347.

KOBAYASHI, Y., YOSHIDA, K., NOGUCHI, M., WAKASUGI, Y., ITO, H. & OKABE, E. (1990). Effect of enflurane on contractile reactivity in isolated canine mesenteric arteries and veins. *Anesth. Analg.,* **70,** 530–536.

LUNDBERG, J.M. (1996). Pharmacology of cotransmission in the autonomic nervous system: integrative aspects on amines, neuropeptides, adenosine triphosphate, amino acids and nitric oxide. *Pharmacol. Rev.,* **48,** 113–178.

LUNN, J.J. & RORIE, D.K. (1984). Halothane-induced changes in the release and disposition of norepinephrine at adrenergic nerve endings in dog saphenous vein. *Anesthesiology,* **61,** 377–384.

MATTHEWS, J.N.S., ALTMAN, D.G., CAMPBELL, M.J. & ROYSTON, P. (1990). Analysis of serial measurements in medical research. *Br. Med. J.,* **300,** 230–235.

MIMAROGLU, C., UTKAN, T., KAYA, T., KAFALI, H. & SARIOGLU, Y. (1994). Effects of propofol on vascular smooth muscle function in isolated rat aorta. *Methods Find. Exp. Clin. Pharmacol.,* **16,** 257–261.

MINAMI, K., YANAGIHARA, N., SEGAWA, K., TSUTSUI, M., SHIGEMATSU, A. & IZUMI, F. (1996). Inhibitory effects of propofol on catecholamine secretion and uptake in cultured bovine adrenal medullary cells. *Naunyn Schmiedebergs Arch. Pharmacol.,* **353,** 572–578.

MULDOON, S.M., VANHOUTTE, P.M., LORENZ, R.R. & VAN DYKE, R.A. (1975). Venomotor changes caused by halothane acting on the sympathetic nerves. *Anesthesiology,* **43,** 41–48.

MULIER, J.P., WOUTERS, P.F., VAN AKEN, H., VERMAUT, G. & VANDERMEERSCH, E. (1991). Cardiodynamic effects of propofol in comparison with thiopental: assessment with a transesophageal echocardiographic approach. *Anesth. Analg.,* **72,** 28–35.

NAKAMURA, K., HATANO, Y., HIRAKATA, H., NISHIWADA, M., TODA, H. & MORI, K. (1992). Direct vasoconstrictor and vasodilator effects of propofol in isolated dog arteries. *Br. J. Anaesth.,* **68,** 193–197.

PARK, K.W., DAI, H.B., LOWENSTEIN, E. & SELLKE, F.W. (1995). Propofol-associated dilation of rat distal coronary arteries is mediated by multiple substances, including endothelium-derived nitric oxide. *Anesth. Analg.,* **81,** 1191–1196.

PARK, W.K., LYNCH, C. & JOHNS, R.A. (1992). Effects of propofol and thiopental in isolated rat aorta and pulmonary artery. *Anesthesiology,* **77,** 956–963.

PETROS, A.J., BOGLE, R.G. & PEARSON, J.D. (1993). Propofol stimulates nitric oxide release from cultured porcine aortic endothelial cells. *Br. J. Pharmacol.,* **109,** 6–7.

PRICE, M.L., MILLAR, B., GROUNDS, M. & CASHMAN, J. (1992). Changes in cardiac index and estimated systemic vascular resistance during induction of anaesthesia with thiopentone, methohexitone, propofol and etomidate. *Br. J. Anaesth.,* **69,** 172–176.

ROBINSON, B.J., BUYCK, H.C.E. & GALLETLY, D.C. (1994). Effects of propofol on heart rate, arterial pressure and digital plethysmograph variability. *Br. J. Anaesth.,* **73,** 167–173.

ROBINSON, B.J., EBERT, T.J., O'BRIAN, T.J., COLINCO, M.D. & MUZI, M. (1997). Mechanisms whereby propofol mediates peripheral vasodilation in humans. *Anesthesiology,* **86,** 64–72.

ROIZEN, M.F., THOA, N.B., MOSS, J. & KOPIN, I.J. (1976). Inhibition by cyclopropane of release of norepinephrine, but not dopamine-beta-hydroxylase, from the guinea-pig vas deferens. *Anesthesiology,* **44,** 54–56.

SAARNIVAARA, L., HILLER, A. & OIKKONEN, M. (1993). QT interval, heart rate and arterial pressures using propofol, thiopentone or methohexitone for induction of anaesthesia in children. *Acta Anaesthesiol. Scand.,* **37,** 419–423.

SELLGREN, J., PONTEN, J. & WALLIN, B.G. (1990). Percutaneous recording of muscle nerve sympathetic activity during propofol, nitrous oxide and isoflurane anesthesia in humans. *Anesthesiology,* **73,** 20–27.

SERVIN, F., DESMONTS, J.M., HABERER, J.P., COCKSHOTT, I.D., PLUMMER, G.F. & FARINOTTI, R. (1988). Pharmacokinetics and protein binding of propofol in patients with cirrhosis. *Anesthesiology,* **69,** 887–891.

STADNICKA, A., FLYNN, N.M., BOSNJAK, Z.J. & KAMPINE, J.P. (1993). Enflurane, halothane, and isoflurane attenuate contractile responses to exogenous and endogenous norepinephrine in isolated small mesenteric veins of the rabbit. *Anesthesiology,* **78,** 326–334.

URABE, M., KAWASAKI, H. & TAKASAKI, K. (1991). Effect of endothelium removal on the vasoconstrictor response to neuronally released 5-hydroxytryptamine and noradrenaline in the rat isolated mesenteric and femoral arteries. *Br. J. Pharmacol.,* **102,** 85–90.

WALLERSTEDT, S.M. & BODELSSON, M. (1997a). Effect of propofol on isolated human omental arteries and veins. *Br. J. Anaesth.,* **78,** 296–300.

WALLERSTEDT, S.M. & BODELSSON, M. (1997b). Endothelium-dependent relaxation by substance P in human isolated omental arteries and vein: relative contribution of prostanoids, nitric oxide and hyperpolarization. *Br. J. Pharmacol.,* **120,** 25–30.

WALLERSTEDT, S.M., TÖRNEBRANDT, K. & BODELSSON, M. (1998). Relaxant effects of propofol on human omental arteries and veins. *Br. J. Anaesth.,* **80,** 655–659.

WIKBERG, J.E.S. & AXELSSON, K.L. (1980). A simple and efficient method for studying neurotransmitter release in vitro by a radiotracer technique. *Acta Physiol. Scand.,* **109,** 123–129.

YAMANOUE, T., BRUM, J.M. & ESTAFANOUS, F.G. (1994). Vasodilation and mechanism of action of propofol in porcine coronary artery. *Anesthesiology,* **81,** 443–451.

(Received March 13, 1998
Revised May 26, 1998
Accepted June 1, 1998)