Effects of propofol on vascular reactivity in isolated aortae from normotensive and spontaneously hypertensive rats†

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We have investigated the effects of propofol 50 µmol litre−1 on contractile and relaxant responses in experimental hypertension and assessed endothelial modulation of these responses. Propofol attenuated norepinephrine-induced contraction of endothelium-intact and endothelium-denuded rings from both Wistar Tokyo (WKY) and spontaneously hypertensive rats (SHR). The effect was significantly greater in endothelium-intact aortae from SHR than in those from WKY rats. Propofol markedly attenuated AVP-induced contraction in aortae from both WKY and SHR. Propofol attenuation of norepinephrine contraction was also observed in rings from both SHR and WKY rats incubated with L-NAME. Propofol attenuation of norepinephrine contraction was suppressed by indomethacin in aortae from SHR but not in those from WKY rats. These results suggest that: (1) propofol attenuated vascular contraction of isolated aortae from SHR in part by a mechanism dependent on events distal to the receptor site (norepinephrine, arginine vasopressin); (2) the effect of propofol on contraction in SHR, observed in the presence of nitric oxide synthase inhibitors but not cyclooxygenase inhibitors, was consistent with either propofol induction of vasodilating cyclooxygenase metabolites from the endothelium or propofol inhibition of vasoconstricting cyclooxygenase metabolites.

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Propofol is a short-acting, widely used i.v. anaesthetic agent.1 In clinical practice, it has been shown that propofol causes hypotension which is mediated by a decrease in systemic resistance2 and/or cardiac output.3 Recently, the role of propofol in vasodilatation has been established under various experimental conditions. Propofol decreased systemic vascular resistance in humans whose cardiac output was controlled by an artificial heart.4 Similarly, in isolated arteries, propofol decreased vascular tone and agonist-induced contraction.5–7 The mechanisms by which propofol relaxes smooth muscle are not completely understood. However, several recent reports5 8 9 suggest that propofol-induced relaxation is partially independent of the endothelium and results from a decrease in intracellular Ca2+ availability in vascular smooth muscle cells. The effect of propofol has been attributed in part to inhibition of Ca2+ influx through voltage- or receptor-gated Ca2+ channels.5 8 From their study on rat aortae using cumulative concentrations of propofol, Park, Lynch and Johns5 suggested that the endothelium modulates vascular responses to propofol by releasing vasodilating cyclooxygenase metabolites and that propofol suppresses endothelium-derived relaxing factor–nitric oxide production.

In arterial hypertension, structural and functional alterations of vessels are implicated in both the pathogenesis and maintenance of hypertension.10–12 Functional studies have shown that there is altered sensitivity to vasoconstrictor agents (i.e. norepinephrine or AVP) depending on the type of vessel.13 14 Acetylcholine induced abnormal relaxation of arteries in patients with essential hypertension15 and in various models of experimental hypertension, including the spontaneously hypertensive rat.16 17 The altered sensitivity of arterial vessels from hypertensive patients or animals to vasoconstrictor or vasodilator agonists could lead to modulation of the effects of propofol.

In this study, we have investigated the effects of propofol on contractile responses after receptor-mediated stimulation, in isolated thoracic aortae from spontaneously hypertensive rats (SHR) and from age-matched Wistar Tokyo (WKY)
rats, used as normotensive controls. In addition, by studying endothelium-dependent and independent relaxant responses, we assessed if the effects of propofol could be modulated by endothelial-released factors.

Materials and methods

Animals and experimental set-up

Experiments were performed on thoracic aortae from male WKY rats and from SHR with established hypertension (18–20 weeks old; Iffa Credo, l’Arbresle, France). All procedures were approved by the Institutional Animal Care and Use Committee. Systolic arterial pressure was measured in unanaesthetized rats, 1 week before the experiment, using the tail-cuff method (Electro Sphygmomanometer PE 300, Narco Biosystems, Houston, TX, USA). Individual values were the mean of six consecutive measurements. Systolic pressure averaged 139±3 mm Hg (n = 16) and 201±2 (n = 16) mm Hg in WKY rats and SHR, respectively (P < 0.001). The rats were anaesthetized briefly with diethyl ether. The thoracic aorta was then excised, cleaned of adherent connective tissue and placed in cold physiological salt solution (PSS) of the following composition (mmol litre–1): NaCl 118.2, KCl 4.7, NaHCO3 25, KH2PO4 1.2, CaCl2 2.5, MgSO4 1.2 and glucose 11.1, and aerated with 95% oxygen and 5% carbon dioxide to give a pH of 7.4.

Thoracic aortae from SHR and WKY rats were cut into rings (2–3 mm long). To analyse endothelium-independent effects of the drug, in some rings the endothelium was removed by gently rubbing the intimal surface with small forceps. In the remaining rings, care was taken not to touch the inner surface of the blood vessel. The rings were suspended horizontally between two L-shaped stainless steel hooks in organ chambers which contained PSS 10 ml maintained at 37°C, as described previously.18 Isometric tension (g) was measured using a force displacement transducer (F60 Myograph, Narco-Biosystems) connected to the upper hook. Aortic rings were stretched to obtain a passive force of 2 g (determined to be optimal in preliminary length–tension experiments) and then allowed to equilibrate for 90 min. During this incubation period, the buffer was changed every 15 min. The rings were then exposed to norepinephrine 0.1 μmol litre–1. Endothelial integrity or denudation was confirmed before the experiment by testing acetylcholine (1 μmol litre–1)-induced relaxation under norepinephrine (0.1 μmol litre–1)-precontracted conditions. After this procedure, the rings were washed and allowed to re-equilibrate to baseline tension for 45 min.

Experimental procedures

For all vessels, cumulative concentration–response curves to agonists were performed without propofol, and then repeated with propofol 50 μmol litre–1 which was incubated with the vessels for 20 min before construction of the curve. Preliminary studies showed that vascular reactivity was not altered by repetition of agonist stimulation and that propofol did not modify basal tension of rings from both SHR and WKY aortae during the time course of incubation before addition of agonists. Propofol was used in its commercially available 10% Intralipid emulsion (56 mmol litre–1 or propofol 10 mg ml–1, 10% soybean oil, 2.25% glycerol, 1.2% purified phospholipid). The propofol concentration of 50 μmol litre–1 was chosen because in our pilot study it induced 50% relaxation in KCl 40 mmol litre–1-contracted aortic rings (data not shown). In some rings, 10% Intralipid was used in place of propofol to evaluate the effect of the solvent. No effect of Intralipid was observed on either basal tension or agonist responsiveness. Vascular reactivity was studied in parallel rings from WKY and SHR aortae to standardize for differences in agonist activity.

Contractile responses

Cumulative concentration–response curves to the α-adrenergic agonist norepinephrine (0.1 nmol litre–1 to 10 μmol litre–1) were generated in endothelium-intact and endothelium-denuded rings. Some endothelium-intact rings were incubated with L-NAME 0.3 mmol litre–1 (n = 5), a nitric oxide synthase inhibitor, and some with indomethacin 10 μmol litre–1 (n = 5), a cyclooxygenase inhibitor. Aortic rings were incubated for 20 min with each inhibitor which was present during the dose–response curve to norepinephrine. In addition, concentration–response curves to AVP 0.01 nmol litre–1 to 0.3 μmol litre–1 were performed in other endothelium-intact rings.

Vasorelaxant responses

Endothelium-intact arteries were precontracted with a norepinephrine concentration that induced 80% maximal contraction of each vessel (0.1 μmol litre–1). Cumulative concentration–response curves to the endothelium-dependent relaxant agonist acetylcholine 1 nmol litre–1 to 0.1 mmol litre–1 with and without propofol 50 μmol litre–1 were performed in rings without inhibitors and in other rings with L-NAME 0.3 mmol litre–1 (n = 4) or indomethacin 10 μmol litre–1 (n = 4). Concentration–response curves to the endothelium-independent agonist nitroprusside (SNP, 0.01 nmol litre–1 to 10 μmol litre–1) were also performed in endothelium-denuded rings.

Drugs

The following drugs were obtained from Sigma Chemical (La Verpillière, France): L-norepinephrine hydrochloride, acetylcholine chloride, N6-nitro-L-arginine methyl ester, indomethacin, arginine vasopressin acetate and sodium nitroprusside. Drugs were dissolved in distilled water, except indomethacin which was dissolved in Na2CO3 (final concentration 50 μmol litre–1) and sonicated before use. Propofol was purchased from Zeneca (Cergy, France) and Intralipid from Pharmacia (Saint-Quentin-Yvelines, France). Drug concentrations are expressed as final molar concentrations in the organ bath.
Fig 1 A: Concentration–response curves to norepinephrine in isolated endothelium-intact aortae from WKY rats (n=8) with (■) and without (□) propofol 50 µmol litre ^{-1} and in endothelium-intact aortae from SHR (n=8) with (●) and without (○) propofol. B: Concentration–response curves to arginine vasopressin in isolated endothelium-intact aortae from WKY rats (n=8) with (■) and without (□) propofol and from SHR (n=8) with (●) and without (○) propofol. Values are mean (SEM).

Data analysis
All values are expressed as mean (SEM). In all experiments, the number of rats from which blood vessels were obtained was eight, unless otherwise indicated. The concentration of the drug (expressed as negative log molar) evoking 50% contraction (pD2 value) or relaxation (pIC50 value) and the value of maximal contraction or maximal relaxation (expressed as a percentage of a previous contraction to the agonist norepinephrine) were calculated using a non-linear iterative curve-fitting procedure (GraphPad Software, San Diego, CA, USA). Statistical evaluation of the data was performed by two-way analysis of variance (ANOVA) for repeated measures to compare the concentration–response curves to agonists. When the F value was significant, differences in pD2 values, pIC50 values and maximal values (Emax) were assessed using the Newman–Keuls or Mann–Whitney post hoc test for significance, as appropriate. Differences between means were considered statistically significant when P<0.05.

Results
Effects of propofol on norepinephrine- and AVP-induced contraction
Cumulative doses of norepinephrine and AVP evoked concentration-dependent contractile responses in endothelium-intact rings in WKY and SHR. Rings from SHR were significantly less sensitive to norepinephrine than those from WKY (P<0.05), but maximal responses elicited by norepinephrine were not different (Fig. 1A). In contrast with norepinephrine, maximal tension induced by AVP was significantly higher in isolated aortae from SHR than in those from WKY rats (2.68 (0.17) vs 0.98 (0.12) g, respectively; P<0.01) (Fig. 1B).

Propofol decreased significantly norepinephrine-induced responses in endothelium-intact aortic rings from both WKY and SHR. Propofol decreased significantly the sensitivity to norepinephrine (pD2 values) in both strains (6.99 (0.12) vs 7.60 (0.11) (P<0.001) in WKY; 6.37 (0.07) vs 7.03 (0.10) (P<0.001) in SHR) and decreased significantly maximal responses in SHR (0.70 (0.12) vs 1.94 (0.22) g; P<0.001) but not in WKY rats (1.60 (0.17) vs 2.04 (0.14) g) (Fig. 1A). Genetic hypertension significantly affected the maximal effect of propofol on norepinephrine-induced contraction (two-way ANOVA, P<0.05). Propofol markedly inhibited AVP-induced contraction in endothelium-intact aortae in both groups (Emax 0.07 (0.03) in WKY, 0.11 (0.04) in SHR) (Fig. 1B).

Influence of endothelium on propofol-induced attenuation of norepinephrine contractions
Removal of the endothelium increased significantly the contractile response to norepinephrine in both strains by increasing pD2 values in WKY (8.64 (0.16) vs 7.60 (0.11); P<0.05) (Fig. 2A, B) and SHR (8.13 (0.10) vs 7.03 (0.10); P<0.05) (Fig. 2E, F). In WKY rats, propofol depressed significantly norepinephrine-induced contraction in aortae without endothelium, by decreasing pD2 values (7.78 (0.06) vs 8.64 (0.16); P<0.01) (Fig. 2B). Propofol did not significantly modify maximal responses (2.23 (0.11) vs 2.41 (0.09) g) (Fig. 2B). Removal of the endothelium did not influence the attenuating effect of propofol on norepinephrine-induced contraction (two-way ANOVA). In SHR, propofol depressed significantly norepinephrine-induced contraction in aortae without endothelium, by decreasing pD2 values (7.55 (0.04) vs 8.13 (0.10); P <0.01) (Fig. 2F). Propofol did not significantly modify the maximal response (2.19 (0.11) vs 2.34 (0.11) g) (Fig. 2F). However, the presence of endothelium significantly affected the attenuating effect of propofol on norepinephrine-induced contraction (two-way ANOVA, P<0.05).

L-NAME increased significantly norepinephrine-induced contraction in endothelium-intact aortae from both WKY (Fig. 2C) and SHR (Fig. 2C). In the presence of L-NAME,
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**Fig 2** Concentration–response curves to norepinephrine in isolated aortae from WKY rats (A, B, C, D) and from SHR (E, F, G, H). A, E: Concentration–response curves to norepinephrine in isolated endothelium-intact (Ec+) aortae (n=8) with (■) and without (□) propofol 50 µmol litre⁻¹; B, F: Concentration–response curves to norepinephrine in isolated endothelium-denuded (Ec–) aortae (n=8) with (■) and without (□) propofol; C, G: Concentration–response curves to norepinephrine in isolated endothelium-intact aortae (n=4) after incubation with L-NAME 0.3 mmol litre⁻¹ for 20 min with (■) and without (□) propofol; D, H: Concentration–response curves to norepinephrine in isolated endothelium-intact aortae (n=5) after incubation with indomethacin 10 µmol litre⁻¹ for 20 min with (■) and without (□) propofol. Values are mean (SEM).

Propofol decreased pD₂ values in aortic rings from WKY (8.09 (0.44) vs 9.58 (0.36); P<0.05, n=4) (Fig. 2c) and SHR (7.55 (0.14) vs 8.15 (0.15), P<0.05, n=4) (Fig. 2g) without affecting maximal contraction of aortae to norepinephrine in WKY (1.82 (0.22) vs 2.18 (0.38)g) (Fig. 2c) or SHR (1.96 (0.43) vs 2.24 (0.40) g) (Fig. 2g).

Indomethacin did not modify norepinephrine-induced contraction in endothelium-intact aortae from either WKY or SHR: dose–response curves to norepinephrine under control conditions and after pretreatment with indomethacin were superimposed (Fig. 2d, h). In WKY endothelium-intact rings, in the presence of indomethacin, propofol caused a significant decrease in tension in response to norepinephrine by decreasing pD₂ values (7.64 (0.13) vs
8.21 (0.25); n=5, P<0.05) (Fig. 2d). In contrast, in intact rings from SHR, the attenuating effect of propofol on norepinephrine-induced contraction was inhibited in the presence of indomethacin (pD2 7.29 (0.07) vs 7.47 (0.09); n=5) (Fig. 2h). In SHR, indomethacin significantly modified the effect of propofol on norepinephrine-induced contraction (two-way ANOVA, P<0.05).

**Effect of propofol on vasorelaxant responses**

In WKY rats, acetylcholine evoked concentration-dependent relaxation of intact rings contracted with norepinephrine 0.1 µmol litre⁻¹. In contrast, in SHR, the response to acetylcholine was biphasic: relaxation was produced at concentrations of 1 nmol litre⁻¹ to 0.3 µmol litre⁻¹ and contraction at higher concentrations (>0.3 µmol litre⁻¹) (Fig. 3a). At the lowest concentrations of acetylcholine, propofol attenuated relaxation by decreasing the sensitivity to acetylcholine in WKY rats (pIC50 6.76 (0.03) vs 7.48 (0.05); P<0.05) and in SHR (pIC50 6.89 (0.06) vs 7.61 (0.04); P<0.05). At the highest concentrations of acetylcholine, propofol improved the impaired relaxation observed in the SHR group by increasing maximal relaxation (87.0 (2.6)% vs 53.1 (3.0)%; P<0.05), but did not modify maximal relaxation in the WKY group (70.8 (2.2)% vs 72.4 (1.3%)) (Fig. 3). Indomethacin prevented the contraction induced by high concentrations of acetylcholine (P<0.05) in SHR. In the presence of indomethacin, propofol attenuated acetylcholine-induced contraction in both strains: sensitivity to acetylcholine was decreased significantly (P<0.05) (pIC50 6.75 (0.08) vs 7.36 (0.09) and 6.80 (0.04) vs 7.48 (0.03) in WKY and SHR rings, respectively); maximal responses to acetylcholine were also decreased significantly (P<0.05) (57.3 (7.2)% vs 80.1 (4.7)%; 75.0 (4.5)% vs 91.8 (2.0)% in WKY and SHR rings, respectively) (Fig. 3b). In the presence of L-NAME, acetylcholine 0.1 mmol litre⁻¹ induced contraction in both strains with no significant differences between tension values. Addition of propofol inhibited acetylcholine-induced contraction in aortic rings from SHR (–1.35 (3.8)% vs 10.3 (1.5%); P<0.05) with no effect in WKY rats (7.9 (2.2)% vs 5.9 (1.7%)) (Fig. 3c).

SNP evoked concentration-dependent relaxation in both strains; relaxation was significantly more pronounced in aortae from SHR than in those from WKY rats (P<0.05) (Fig. 4). Propofol increased slightly nitroprusside-induced relaxation of rings from SHR. pIC50 values were significantly greater in the presence of propofol (8.64 (0.05) vs 8.37 (0.05); P<0.05). In aortae from WKY, propofol did not modify the magnitude of SNP-induced relaxation (pIC50 8.07 (0.08) vs 8.11 (0.06)).

**Discussion**

Our study was designed to assess the effects of propofol on in vitro vascular reactivity in aortae from SHR and WKY rats. Propofol differentially modulated contractile and relaxant responses of isolated aortae from SHR compared with those from WKY rats. Furthermore, propofol impaired vascular reactivity in SHR in part via an endothelium-dependent mechanism in which cyclooxygenase and nitric oxide synthase pathways may be involved.

In agreement with previous reports,5 6 8 19 we demon-
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Fig 4 Concentration–response curves to sodium nitroprusside (SNP) in isolated endothelium-denuded aorta from WKY rats (n=8) with (●) and without (□) propofol 50 µmol litre⁻¹ and in isolated aortae from SHR (n=8) with (○) and without (●) propofol. Values are mean (SEM).

strated that propofol attenuated contractile responses to α-receptor agonists in arteries from normotensive rats. Our results showed that propofol also attenuated contraction to another receptor agonist, AVP, a finding which has not been reported previously. We have demonstrated for the first time that propofol induced inhibition of norepinephrine- and AVP-induced contraction in aortae from SHR. Inhibition of norepinephrine responses was of a greater magnitude than that observed in aortae from WKY. Similar findings have been reported by Nakamura and colleagues20 with thiobarbiturates in phenylephrine-contracted aortic strips from SHR with established hypertension, suggesting that contractile responses of aortae from SHR are more sensitive to the effects of i.v. anaesthetic agents than those from WKY rats.

In SHR, several alterations in vascular cellular events resulting in abnormal functioning have been demonstrated which could account for the difference in propofol effects between SHR and WKY rats. These alterations include changes in responsiveness of vascular smooth muscle cells to receptor agonist,21 increase in cytosolic Ca²⁺ concentrations22 and impairment of endothelial function.23 In blood vessels from normotensive rats, propofol caused a decrease in Ca²⁺ influx via either voltage-gated Ca²⁺ channels or receptor-mediated channels, or both, depending on the predominant presence of either channel.8 9 Norepinephrine and AVP both induce contractile responses in vascular smooth muscle cells via specific receptors that are linked to G protein and coupled to phospholipase C activation. This activation results in release of stored Ca²⁺ from the sarcoplasmic reticulum. In addition, a Ca²⁺ entry step has been observed for norepinephrine24 and AVP.25 It was hypothesized recently that influx of extracellular Ca²⁺ was more important for the constrictor effect of AVP than that for α₁ adrenoceptors, which depend more on Ca²⁺ released from internal stores.26 The predominating effect of propofol, observed in both strains, on AVP compared with norepinephrine stimulation is in agreement with this hypothesis.

Moreover, the inhibitory effect of propofol on contractions induced by both norepinephrine and AVP receptor-mediated agonists, suggests that the effect of propofol depends, at least in part, on events distal to the receptor site.

In our study, when endothelium was present, propofol attenuated contractility induced by norepinephrine more in vessels from SHR than in those from WKY rats. In SHR, the attenuating effect of propofol on norepinephrine-induced contractility, in the absence of endothelium, was less than that in aortae with intact endothelium. These findings suggest that in SHR, part of the relaxing effect of propofol may be mediated by the endothelium. This greater inhibition of norepinephrine-induced contraction could be explained in two ways: (1) release of an endothelium-derived relaxing factor is enhanced by propofol or (2) release of an endothelium-derived contracting factor is attenuated by propofol.

The effect of propofol was assessed further using L-NAME, an inhibitor of nitric oxide synthase. Attenuation of the contractile response to norepinephrine in aortae from SHR was still present, suggesting that release of nitric oxide may not be implicated in the effect of propofol. However, the lower degree of attenuation requires confirmation. In contrast, in the presence of indomethacin, the inhibitory effect of propofol on the contractile response to norepinephrine was suppressed in SHR whereas it was still observed in WKY rats. These findings suggest that in aortae from SHR, the cyclooxygenase pathway was implicated in the attenuating effect of propofol in norepinephrine-induced contraction. Our study did not clarify whether or not release of a relaxing factor or inhibition of a contracting factor derived from the cyclooxygenase pathway was involved.

In the second part of our study, we investigated the effects of propofol on endothelium-dependent and endothelium-independent relaxation in isolated aortae from SHR and WKY rats. In arteries from normotensive rats, propofol attenuated acetylcholine-induced relaxation. Moreover, this attenuation was still observed in the presence of a cyclooxygenase inhibitor. Acetylcholine induces release of nitric oxide which then relaxes vascular smooth muscle via stimulation of soluble guanylate cyclase and increase in intracellular cyclic guanosine monophosphate (cGMP).27 Our results suggest that propofol attenuation of acetylcholine-induced relaxation involves the nitric oxide–cGMP pathway. Previous experiments using isolated arteries have demonstrated that not only propofol28 but other anaesthetic agents with different chemical formulae, including volatile anesthetics,29 30 barbiturates31 and local anaesthetics,32 inhibit endothelium-dependent relaxation. Moreover, we found that propofol did not stimulate or inhibit SNP-induced relaxation. SNP releases exogenous nitric oxide, activates soluble guanylate cyclase and increases intracellular concentrations of cGMP, thus inducing relaxation independent of the endothelium.33 Our results, based on mechanical experiments only, do not agree with those of Miyawaki and colleagues28 whose studies with both acetylcholine and SNP suggest suppression of nitric oxide in the smooth muscle.
cell itself by propofol 3–30 µmol litre⁻¹. In contrast, using endothelial-vascular smooth muscle cell co-cultures, Johns and colleagues 34 observed inhibition of relaxation by halothane and isoflurane only in the presence of endothelium. Our findings in normotensive rats are in agreement with this observation; propofol appeared to inhibit endothelial nitric oxide synthase activity but not smooth muscle guanylate cyclase activity.

In aortae from SHR, propofol attenuated acetylcholine-induced endothelium-dependent relaxation in the same manner as in those from WKY rats. However, propofol reversed endothelium-dependent contraction in response to high concentrations of acetylcholine. Endothelium-dependent contraction induced by high concentrations of acetylcholine observed in SHR aortae is believed to be caused by increased production of PGH₂, an endoperoxide precursor of contracting prostaglandins and/or augmented sensitivity of SHR smooth muscle to this contracting factor. 35 Our results, obtained after pretreatment of aortae from SHR with indomethacin which demonstrated enhancement of relaxation with acetylcholine, support the hypothesis that an endothelial prostaglandin is involved in acetylcholine-induced contraction. Inhibition by propofol of acetylcholine-induced endothelium-dependent relaxation was unmasked after effective inhibition of the cyclooxygenase pathway. In contrast, the effect of propofol on acetylcholine-induced relaxation was assessed after incubation of rings from SHR with an inhibitor of nitric oxide synthase. In this case, acetylcholine-induced contraction was inhibited by propofol. These results suggest that in aortae from SHR, propofol inhibited the release and/or production of contracting factors derived from the cyclooxygenase pathway. Nitrovasodilator-induced relaxation was more pronounced in SHR than in WKY rats. This finding is in agreement with the results of Papapetropoulos and colleagues 36 who observed greater production of cGMP in SHR aortic rings than in those from WKY after stimulation with SNP. Propofol increased this relaxation and to our knowledge there are no data which confirm or dispute this result, observed only in SHR. However, the effects of propofol on the two enzyme systems (nitric oxide synthase and guanylate cyclase) resulted in a decrease in vascular relaxation. This suggests that after administration of propofol, production of cGMP after SNP–guanylate cyclase stimulation compared with inhibition of nitric oxide was not sufficient to induce relaxation.

Our results were obtained with supraclinical concentrations of propofol (50 µmol litre⁻¹). In clinical practice, typical peak serum concentrations are approximately 44 µmol litre⁻¹, but free drug concentrations are reduced markedly by 97% protein binding. Therefore, extrapolation of our findings to the clinical situation must be made with caution.

In summary, our results confirmed that propofol differentially altered vascular contractile and relaxant responses to agonists in SHR and WKY rats. In SHR, the attenuating effect of propofol on contraction partially involved endothelium via the cyclooxygenase pathway. The effects of propofol on relaxation were complex and resulted from inhibition of the nitric oxide synthase pathway, inhibition of release of vasocontracting metabolites and stimulation of the guanylate pathway.

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