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Role of L-type calcium channels in altered microvascular responses to propofol in hypertension

B. K. Lawton[1,2], N. J. Brown[1], C. S. Reilly[2] and Z. L. S. Brookes[1,2]*

[1] Microcirculation Research Group and [2] Academic Unit of Anaesthesia, Faculty of Medicine, Dentistry and Health, University of Sheffield, Beech Hill Road, Sheffield S10 2RX, UK

* Corresponding author. E-mail: zoe_brookes@yahoo.ca and zoe.brookes@students.pcmd.ac.uk

Editor's key points

- Propofol is an L-type calcium channel (LTCC) antagonist.
- Rat mesenteric microcirculation was assessed in response to propofol and an LTCC agonist.
- Propofol decreased arterial pressure and induced relaxation of mesenteric microvessels.
- These effects were greater in spontaneously hypertensive rats.
- This may have clinical implications for hypertensive patients.

Background. Propofol acts as an L-type calcium channel (LTCC) antagonist to decrease peripheral resistance and initiate hypotension. This study investigated LTCC sensitivity/expression in hypertension and the role of LTCCs in exaggerated hypotension to propofol in this situation.

Methods. Age-matched 12- to 15-week-old normotensive rats [male Wistar Kyoto (WKY)] and spontaneously hypertensive rats (SHR) were used. Propofol (10 mg kg^{-1}, 10–50 mg kg^{-1} h^{-1} i.v.) was administered and the mesenteric microcirculation (<70 μm) observed with fluorescent *in vivo* microscopy using fluorescein isothiocyanate-conjugated bovine serum albumin (100 mg kg^{-1} i.v.). Western blotting was used to measure tissue expression of the α_{1C} LTCC subtype. Pressure myography was used to assess isolated mesenteric arterioles (<350 μm) in response to BAYK8644 (0.1 nM–1 μM), a specific LTCC channel agonist.

Results. Propofol dilated isolated arterioles {336.6 μM [mean (SD) change 16.2 (5.8)%]}. However, constriction to BAYK8644 was reduced at this concentration of propofol [EC_{50}=8.3 (0.1) log mol^{-1}] compared with controls [7.4 (0.1) log mol^{-1}, $P<0.05$], suggesting that propofol inhibited LTCCs. The sensitivity of LTCCs increased during hypertension, as *in vivo* there was a greater increase in mean arterial pressure (MAP) to BAYK8644 [10 μg kg^{-1}, WKY: 59.5 (9.3)%; SHR: 97.7 (6.3)%, $P<0.05$] with exaggerated constriction of arterioles [10 μg kg^{-1}, WKY: 9.1 (2.5)%; SHR: 19.1 (2.6)%, $P<0.05$]. Propofol also decreased MAP in SHR over time ($P<0.05$), but remained unchanged in WKY. Using western blotting, expression of α_{1C} was greater in SHR compared with WKY ($P<0.05$).

Conclusions. Propofol acts via LTCC channels, with increased channel expression and sensitivity in genetically hypertensive rats. We suggest that increased sensitivity and expression of LTCCs may be a mechanism for exaggerated hypertension during propofol anaesthesia.

Keywords: anaesthetics i.v., propofol; calcium channel blockers; hypertension, arterial pressure; microvessels, microvascular network

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Propofol (2,6-dispropylphenol) is a short-acting and widely used i.v. anaesthetic agent,[1] which also causes a decrease in arterial pressure due to reduced systemic vascular resistance.[2 3] However, when a patient has underlying hypertension, acute hypotension is exaggerated and can be potentially fatal.

In rodents, propofol causes dilatation of skeletal muscle arterioles and venules (<200 μm) *in vivo*.[3 4] Orthogonal polarization spectral imaging has also demonstrated reduced perfusion of the sublingual microcirculatory network in humans.[5] Propofol exerts direct vasodilator effects via inhibition of L-type calcium channels (LTCCs) in the rat aorta and rabbit arterioles (~70–100 μm).[6 7] In the neuronal tissue and cardiac muscle, the LTCC dihydropyridine-binding site is bound by propofol,[8–10] but this has yet to be confirmed in the vasculature. It is important to study the microcirculation independently as physiological control mechanisms may differ from those in larger-sized vessels.[4]

Within the vasculature, calcium (Ca^{2+}) movement is altered during hypertension, as demonstrated by several patch clamping studies identifying greater Ca^{2+} current densities in mesenteric vascular smooth muscle cells (VSMCs) from spontaneously hypertensive rats (SHR) aged 6–20 weeks.[11–14] Increased mRNA and protein expression of the α_{1C} subunit of the LTCC has been demonstrated in mesenteric arteries from 12- to 15-week-old SHR.[15] It may

be that in the SHR model of hypertension, there is remodelling of the molecular composition of Ca_V channels.[16] The role of LTCCs during hypertension has yet to be elucidated *in vivo* or studied within the microcirculation.

Considering that propofol affects microvascular diameters via LTCCs and that hypertension is a disease process possibly characterized by dysfunction of LTCCS,[17] our hypothesis is that exaggerated microvascular responses to propofol anaesthesia are mediated via LTCCs. Similar to humans, our previous *in vivo* studies in rats reported that hypotension and microvascular dilatation, in response to propofol, were exaggerated in hypertensive rats.[4 18] However, the mechanisms remain uncharacterized. Hence, the overall aims of this study were to determine whether (i) the vascular effects of propofol occur via LTCCs, (ii) microvascular LTCC function and expression is altered during hypertension, and (iii) altered responses to propofol during hypertension are mediated via LTCCs. The effects of propofol on the microcirculation could not be determined *in vivo*, as the mesenteric preparation required surgery/anaesthesia, and thus, we did not have a conscious control. Hence, we performed *ex vivo* experiments with isolated vessels, confirming that propofol induced dilation via inhibition of LTCCs, that is, propofol reduced constriction to the LTCC opener methyl,2-6-dimethyl-5-nitro-4[2-(trifluoromethylphenyl]-1-4dihydropyridine-3-carboxylate ($C_{16}H_{15}F_3N_2O_4$), known as BAYK8644. LTCCs are the dominant channels located on VSMCs, and thus when opened, influx of intracellular Ca^{2+} results in VSM constriction.[19] Aims (ii) and (iii) were then investigated using fluorescent intravital microscopy to determine the effects of BAYK8644 on cardiovascular and microvascular variables in SHR and normotensive aged-matched (12–15 weeks) rats (Wistar Kyoto, WKY), anaesthetized with propofol.

Methods

Animals

Male WKY rats and SHR, aged 12–15 weeks ($n=12$ *in vivo* microscopy, $n=34$ myography) were supplied by Harlan and housed in the Biological Services Unit at the University of Sheffield. Food and water were available *ad libitum*. Animals were exposed to a 12/12 h light/dark cycle and housed in groups of two to six before surgery. All procedures were carried out under the Animal Scientific Procedures Act (1986).

Drugs and solutions

The constituents of the HEPES–phosphate-buffered saline (HEPES–PBS) solution were: 0.2884 g litre^{-1} $MgSO_4$, 0.245 g litre^{-1} $CaCl_2$, 2.383 g litre^{-1} HEPES, 8.2983 g litre^{-1} NaCl, 0.3504 g litre^{-1} KCl, and 0.1606 g litre^{-1} KH_2PO_4. On the day of use, 0.99 g litre^{-1} of D(+)-glucose was added to the solution and the pH adjusted to 7.4. All drugs were purchased from Sigma UK unless stated otherwise.

BAYK8644 was dissolved in ethanol and saline (0.9% sodium chloride), and thus, an equivalent volume of ethanol (0.5%) was used as a vehicle. Propofol [Fresenius propofol 1% (10 mg ml^{-1}), Fresenius Kabi Ltd, Warrington, UK] was manufactured in an Intralipid™ suspension comprising soya bean oil (10%), egg phosphatide (1.2%), and glycerol (2.25%); thus, equivalent Intralipid™ (1%, Fresenius Kabi Ltd) vehicle controls were also performed.

At 5°C to avoid denaturing the BSA, 0.0378 g fluorescein isothiocyanate (FITC, F7250) isomer I was conjugated to 2 g bovine serum albumin (BSA, A9647) in 20 ml bicarbonate solution as previously described.[20]

Pressure myography

Surgery

Rats were killed by rapid cervical dislocation followed by immediate removal of the ileum and adjacent mesentery, through a midline laparotomy incision. The mesentery was then transferred onto a dissecting dish and maintained in ice-cold HEPES–PBS solution at 4°C. A third-order mesenteric arteriole (~300 μm) was then dissected free from the surrounding adipose tissue for observation using myography. Arteries were carefully transferred to the organ bath and mounted on glass cannulae at 60 mm Hg (Living Systems Instrumentation, Burlington, VT, USA). Vessels were then stabilized and maintained as described previously.[21]

Measurements

Vessel diameter (lumen, thus excluding vessel wall) and right and left wall thickness were assessed 4 min after the addition of 0.1 nM–1 μM BAYK8644 to the bath using the video dimension analyser (Living Systems Instrumentation). The wall:lumen ratio could thus be calculated.[21] The EC_{50} (drug concentration required to elicit a half maximal response) and E_{max} (% constriction at maximal response) were determined using GraphPad Prism.

Protocol

Dose–response curves were obtained in the presence of 0, 3.4, 33, and 336.6 μM propofol added 5 min before BAYK8644 (WKY, $n=6$). Appropriate vehicle controls were performed replacing BAYK8644 with 0.5% ethanol or BAYK8644 in the presence of 1% Intralipid™ rather than propofol to ensure that diameters were unaffected ($n=12$). Time controls were also performed, whereby BAYK8644 dose–response curves without propofol were repeated four to five times to ensure consistency over the duration of the experimental protocol ($n=10$).

At the end of all experiments, vessel viability was confirmed. To induce vasoconstriction, 5 mM phenylephrine (PE) was added, and then 1 min after PE, 5 μM acetylcholine (ACh) was added to produce vasodilatation. Vessels that constricted >100 μm in response to PE and dilated >100 μm in response to ACh were considered to have viable smooth muscle cells and an intact endothelium, respectively.

In vivo microscopy

Surgery

During brief sedation with halothane (<1 min), i.v. anaesthesia was induced with a bolus dose of propofol (10 mg kg^{-1}) via the ventral tail vein, followed by maintenance with a continuous infusion of 10–50 mg kg^{-1} h^{-1} by the same route. Adequate depth of anaesthesia was determined by loss of the pedal withdrawal reflex in response to nociceptive stimulus, while maintaining a stable heart rate and mean arterial pressure (MAP) >90 mm Hg. This dose regimen results in consistent plasma concentrations of propofol and blood gases as described previously.[22] A tracheostomy was then performed and an oesophageal thermometer placed, to ensure core body temperature remained at 36 (1°C). The right jugular vein was cannulated for administration of FITC-BSA (100 mg kg^{-1} body weight) and the left carotid artery for computerized recording of arterial pressure using WINDAQ (DI-400, DATAQ Instruments, Akron, OH, USA). Finally, a laparotomy was performed and a small section of the mesentery exteriorized (~10 cm) for observation of microvessels in mesenteric windows using *in vivo* microscopy.[22]

Image analysis

Fluorescent images (illuminated with blue light, 460–90 nm) of the microcirculation were viewed on a high-resolution monitor (PVM-1443, Sony, UK) via a ×20 objective (0.30 numerical aperture, Leica, UK) and 13 W black and white CCD camera (Hitachi, UK: 752×582 pixels) attached to a Nikon Optiphot-2 microscope (Nikon Ltd, Kingston, Surrey, UK). Areas of interest (AOIs) were then recorded onto DVD^{+} using a DVD recorder at 25 frames s^{-1} (Datavideo MP6000, Glossop, UK: 720×480 lines), for later off-line computerized image analysis with IPPROPLUS™ (ImageSolutions, Preston, UK).[23] One AOI containing an arteriole (15–40 μm) and a venule (25–70 μm) was selected during the equilibration period (−30–0 min) and recorded for 30 s every 10 min for the experimental duration (t=0–60 min).

Measurements

Cardiovascular variables (MAP and heart rate) were recorded every 10 min, 1 min before BAYK8644, and at the maximum response to BAYK8644, which occurred 30 s post-administration. Concurrently, vessel diameter and macromolecular leak were measured from fluorescent images using IPPROPLUS™.[23] All variables were expressed as a percentage change (%Δ) at each dose of BAYK8644 compared with baseline (t=0).

Protocol

FITC-BSA (100 mg kg^{-1}, i.v.) was given at t=−10 min. After this, 0.1, 0.5, 1.0, 5.0, and 10 μg kg^{-1} (0.1 ml vol. 100 g^{-1}, i.v.) BAYK8644 were then administered during propofol anaesthesia (WKY n=6, SHR n=6) every 10 min during the experimental period (t=0–60).

Western blot

At the end of each study, mesenteric microvessels and their surrounding connective tissues were carefully dissected from the ileum, snap frozen and then stored in liquid nitrogen. When required, pooled samples (n=4) from both WKY and SHR strains were homogenized on ice with 1 ml of triple detergent lysis buffer. Large tissue debris and nuclear fragments were removed by a centrifuge spin of 1000*g* for 10 min, the supernatant removed, and then spun again at 14 000*g* for 15 min at 4°C. Finally, the supernatant was spun at 100 000*g* for a further 1 h at 4°C. The resulting pellet was re-suspended in 200 μl of lysis buffer. Protein concentration was determined by the bicinchoninic acid protein assay. Protein was loaded on a Nupage 3–8% Tris acetate gel for electrophoresis (PAGE) and transferred onto 0.45 μM nitrocellulose membranes for 3 h at 100 mA using Tris acetate sodium dodecyl sulphate buffer with Novex antioxidant added. Non-specific antibody binding to the membrane was blocked with 10% non-fat milk in Tris buffered saline (TBS)–Tween 20 (TBST, 0.1%, v/v) overnight at 4°C. Membranes were then incubated with rabbit Anti-$Ca_v1.2$ (1:333; Alamone Labs Ltd, Jerusalem) in 10% milk/TBST overnight at 4°C, followed by 5 h at room temperature. The membrane was then washed 4× 10 min in TBST. After incubation with the horseradish peroxidase-conjugated anti-rabbit secondary antibody (1 in 5000), bands were then developed using enhanced chemiluminescence and visualized on X-ray film. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as a protein loading control with the primary antibody at 1:4000 and the secondary antibody at 1:10 000 dilutions, respectively, both in 1% milk. GS-710 software was then used to measure the peak density of $Ca_v1.2$ (α_{1C}) and GAPDH bands, with the results expressed as a ratio.

Statistical analysis

MAP, vessel diameter, and macromolecular leak were expressed as mean (SD). Parametric data analysis was performed as the data were normally distributed, as assessed using Graph Pad Prism 5. For analysis of within-group variation, a one-way analysis of variance (ANOVA) was used. Between-group variation in all studies was assessed using ANOVA, with a Dunnett's multiple comparison or the Bonferroni post-test as appropriate, and significance was assumed with values of P<0.05.

Results

Vascular effects of propofol *ex vivo*

Vessel diameter

Propofol caused dose-dependent dilatation of isolated WKY arterioles at 3.4 μM [mean (SD) 4.1 (5.1)%] and 33.7 μM [9.5 (6.0)%], reaching significance at 336.6 μM [16.2 (5.8)%, P<0.05].

Propofol reduced constriction of WKY arterioles to BAYK8644 between 3 and 30 nM BAYK8644, with the EC_{50} of BAYK8644. In the presence of 336.6 μM propofol,

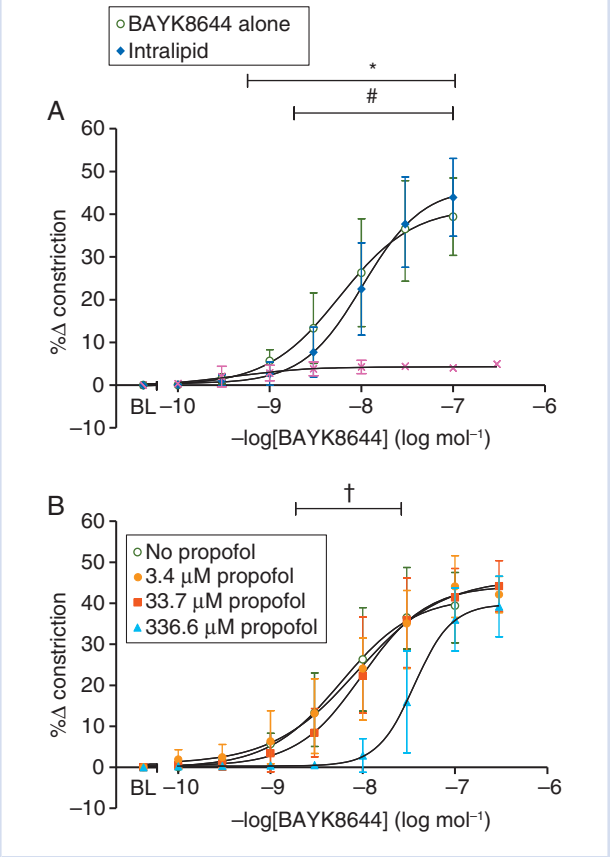


Fig 1 (A) Dose-dependent percentage constriction from baseline of isolated rat mesenteric arterioles (~300 μm) determined using pressure myography. Responses in the presence of BAYK8644 alone, Intralipid, or BAYK8644 replaced by equivalent dose of ethanol vehicle (pink cross) for normotensive (WKY, $n=6$) rats. $P<0.05$ *BAYK844 and #Intralipid *vs* ethanol. (B) Reduced constriction to BAYK8644 with increased concentrations of propofol [no propofol; 3.4, 33.7, and 336.6 μM propofol] in normotensive (WKY, $n=6$) rats. †$P<0.05$ *vs* control (no propofol).

constriction was significantly higher than without propofol [8.3 (0.2) and 7.4 (0.2) log mol^{-1}, respectively] (Fig. 1). However, the E_{max} values were not significantly different [E_{max}: 36.0 (6.9)% without propofol and 41.6 (9.7)% with 336.6 μM propofol], indicating competitive antagonism.

Cardiovascular and microvascular responses during hypertension *in vivo*

Arterial pressure

MAP was higher in SHR than in WKY at baseline: 138.3 (14.1) and 110.8 (21.7) mm Hg, respectively ($t=0$, $P<0.05$). BAYK8644 caused a dose-dependent increase in MAP ($P<0.05$, 1–10 μg kg^{-1}), which was greater in SHR than in WKY, particularly at higher doses of 5 and 10 μg kg^{-1} ($P<0.05$: SHR *vs* WKY; Fig. 2A).

Vessel diameter *in vivo*

SHR exhibited smaller arteriolar [$t=0$, WKY: 35.6 (12.3) μm; SHR: 21.2 (3.8) μm] and venular [$t=0$, WKY: 58.5 (26.2) μm; SHR: 34.0 (10.3) μm] diameters at baseline. Significant constriction of arterioles (0.5–10 μg kg^{-1}) and venules (1–10 μg kg^{-1}) occurred with BAYK8644 ($P<0.05$) and was more pronounced in arterioles from SHR than WKY ($P<0.05$; Fig. 2B and C).

Microvascular leak

BAYK8644 did not appear to alter macromolecular leak from post-capillary venules in either WKY or SHR (Fig. 2D).

Expression of α_{1C} protein (subunit of LTCC)

Western blotting demonstrated the presence of 240 kDa bands in mesenteric vascular tissue (Fig. 3). The immunoreactive densities for α_{1C} and GAPDH are also shown, with α_{1C} in SHR mesenteric lysates approximately two-fold higher than the WKY, representing increased expression of the LTCC protein.

Microvascular responses during hypertension *ex vivo*

Ex vivo diameters of mesenteric arterioles were less in SHR [259 (18.3) μm] than in WKY [300.9 (4.0) μm] post-stabilization ($P<0.05$); however, the wall:lumen ratio was greater in SHR than in WKY [0.2 (0.0) and 0.1 (0.0), respectively, $P<0.05$]. No significant differences between WKY and SHR were observed for responses to PE and ACh.

Cardiovascular responses to propofol during hypertension *in vivo*

Arterial pressure

Propofol caused a significant decrease in MAP in SHR between 20 and 50 min [$t=50$, 85.8 (13.2) mm Hg, $P<0.05$], but remained unchanged in WKY [$t=50$, 101.7 (15.9) mm Hg] (Fig. 4).

Discussion

This *in vivo* study has determined an important mechanism of propofol-mediated dilatation within the rat mesenteric microcirculation, that is, inhibition of vascular LTCCs. Using the LTCC agonist BAYK8644, we also determined that during hypertension, LTCCs have enhanced physiological function and increased expression within this vasculature. This was confirmed by the exaggerated response to propofol in genetically hypertensive animals.

Our laboratory and others have previously reported that propofol induces microvascular dilatation, in conjunction with its known hypotensive effects.[3 4 24] Studies on rat cerebrocortical membranes suggested that LTCC may be a target for propofol,[9 10] in addition to experiments with isolated mesenteric vessels.[7] In the present study, propofol also inhibited constriction to the LTCC opener BAYK8644 *ex vivo* as anticipated, along with smaller arterioles and venules (<40 μm) *in vivo*, which had not previously been

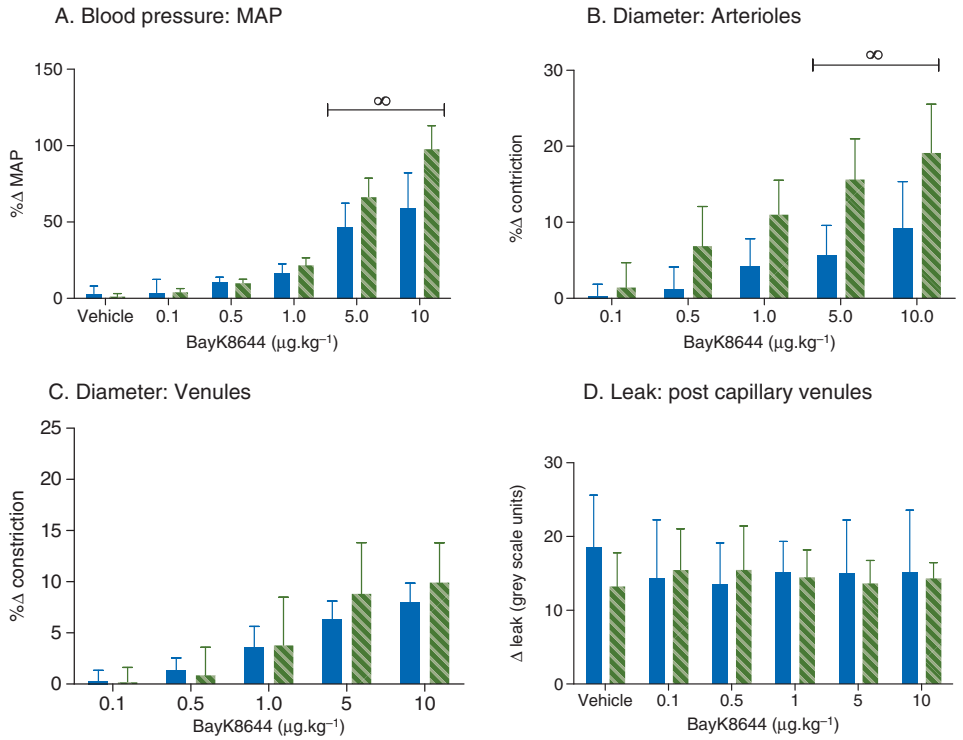
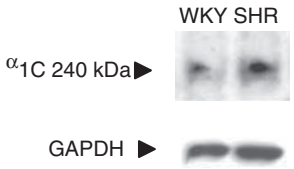


Fig 2 Effect of increasing concentrations of BAYK8644 (0.1–10 μg kg^{-1}) on (A) percentage change in MAP, (B) arteriolar diameter, (C) venular diameter, and (D) macromolecular leak from mesenteric venules *in vivo* in normotensive (WKY, blue bars, $n=6$) and spontaneously hypertensive (SHR, green bars, $n=6$) propofol-anaesthetized rats. $^{\infty}P<0.05$ *vs* WKY.



Exposure time (min)		WKY		SHR	
		1	*2*	*1*	*2*
5	α_{1C}	0.36	1.01	0.66	1.83
	GAPDH	1.04	2.43	1.03	2.37
	Ratio	0.35	0.41	0.64	0.77

Fig 3 Western blots, comparing the densities of the 240 kDa immunoreactive band associated with the α_{1C} protein, in pooled samples from the mesenteric vasculature of normotensive (WKY, $n=4$) and spontaneously hypertensive rats (SHR, $n=4$) (upper photograph). Quantitative analysis of the protein band densities for α_{1C} and GAPDH bands in duplicate samples and the relative ratios are displayed in the table. Samples were analysed on three separate occasions with the same ratio obtained, demonstrating increased α_{1C} protein in SHR rats.

demonstrated. We thus present further evidence that propofol acts as a functional LTCC antagonist within the rat vasculature. Recently, patch-clamp studies in atrial myocytes isolated from cardiac bypass patients demonstrated increased inactivation of the LTCC to propofol; thus, this appears not to be a rodent-specific mechanism.[25] Nevertheless, other vasodilator mechanisms cannot be excluded, as dilatation of mesenteric arterioles to propofol also involves

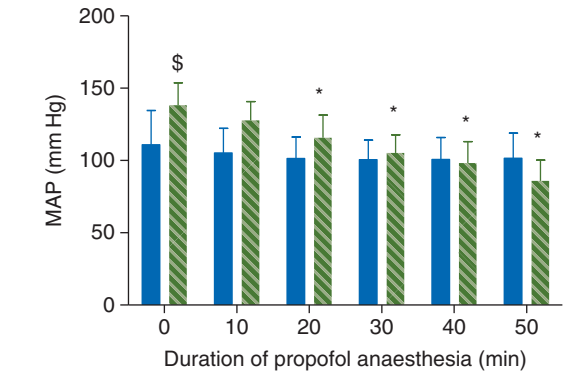


Fig 4 MAP over time during maintenance of propofol anaesthesia (10–50 mg kg^{-1} h^{-1} i.v.) in normotensive (WKY, blue bars, $n=6$) and spontaneously hypertensive (SHR, green bars, $n=6$) rats. $^{\$}P<0.05$ *vs* WKY; $^{*}P<0.05$ *vs* $t=0$.

an endothelial-dependent component, namely nitric oxide.[26] When functioning as an LTCC inhibitor, however, we have also shown that propofol acts as a competitive reversible antagonist, as maximal responses were still elicited with higher doses of BAYK8644. This finding may have implications for clinical use, as a result of interactions with other drug therapies acting on the same mechanisms. For example, nifedipine and amlodipine are commonly used anti-hypertensive drugs also acting on LTCCs, and which patients may often be receiving before anaesthesia.

It is known that hypertension is a disease process typified by altered expression of calcium channels in the vasculature.[14] Our study also investigated altered microvascular function of LTCCs in hypertension, with *in vivo* microscopy experiments determining that constriction to BAYK8644 was exaggerated in the mesenteric microcirculation of 12- to 15-week-old SHR compared with WKY. Our microvascular mesenteric studies *in vivo* (<40 μm) are in agreement with Pratt and colleagues[15] who performed wire myography studies on larger isolated mesenteric arteries *ex vivo* (3 mm length), determining that deleted repetition SHR exhibited greater constriction to BAYK8644 compared with WKY. However, our study is the first to report exaggerated responses to BAYK8644 in SHR *in vivo*. Several patch-clamping studies on isolated mesenteric VSMCs have also suggested enhanced function in SHR is due to either larger Ca^{2+} current densities[13] and/or increased LTCC density and enhanced numbers of channel openings.[11 12] In addition, using western blot analysis of mesenteric tissue from 12- to 15-week-old SHR, there was increased expression of the $Ca_v1.2$ protein, which forms the α_{1C} subunit of LTCC in VSMCs. Our findings are in direct agreement with Pratt and colleagues[15] and confirm altered expression in this particular model, thus supporting our *in vivo* findings. Together, these studies present strong evidence for increased LTCC function and expression, and ultimately increased Ca^{2+} influx into VSMCs during hypertension. It remains to be seen whether humans exhibit similar functional alterations of LTCCs within the microvasculature, particularly as only 10% of hypertensive cases are thought to be genetic in origin, and thus, further human studies are warranted.

Altered expression and function of LTCCs has implications for arterial pressure and microvascular responses to anaesthesia. Indeed, a previous study in our laboratory found that propofol-induced hypotension and arteriolar dilatation were exaggerated in SHR compared with age-matched WKY.[18] The current study can now provide a possible mechanistic basis to these observations, that is, increased function and expression of LTCCs during hypertension, especially as propofol itself may act via LTCCs. Indeed, there is limited evidence for this, as propofol reduced angiotensin II-elicited Ca^{2+} influx into cultured VSMCs.[27]

Following on from investigation of vascular tone and arterial pressure, no differences were identified in microvascular leak between WKY and SHR; therefore, endothelial integrity was not compromised throughout the experimental procedure. In previous studies, however, investigating the skeletal muscle during propofol anaesthesia, there was greater leak from venules within SHR compared with WKY.[18] Calcium channel blockers in general may lead to increased vascular and cell permeability,[28 29] although the mechanisms involved are unknown and require further investigation. Hence, findings from this study suggest that compared with the skeletal muscle, the mesentery may be more resistant to leak via Ca^{2+}-dependent mechanisms. This again requires further clarification.

One limitation of the present study is that unlike the dorsal microcirculatory chamber model,[3 18] the mesenteric microcirculation preparation (requiring anaesthesia and surgery) could not be not recorded before anaesthesia. Nevertheless, in the current study, there were no differences in the doses of propofol given to SHR and WKY,[18] and therefore, depth of anaesthesia is unlikely to explain the decrease in arterial pressure.

In summary, propofol decreases arterial pressure and induces relaxation of mesenteric microvessels by inhibition of LTCCs *in vivo*. These functional physiological responses are exaggerated in hypertensive rats, in conjunction with increased vascular expression of the α_{1C} subunit of LTCCs. Thus, increased expression and function of LTCCs may explain exaggerated arterial pressure and increased dilatation of arterioles with propofol in hypertension.

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Declaration of interest

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