J. Pharm. Pharmacol. 1992, 44: 34–38
Received April 24, 1991

Effects of Anaesthetic Agents on Pressor Response to β-Blockers in the Rat

ALY ABDELRAHMAN, YONG-XIANG WANG AND CATHERINE C. Y. PANG

Department of Pharmacology and Therapeutics, Faculty of Medicine, The University of British Columbia, 2176 Health Sciences Mall, Vancouver, BC, V6T 1Z3 Canada

Abstract—It has been shown that paradoxical pressor response to a β-adrenoceptor antagonist occurs in conscious rats pretreated with an α-adrenoceptor antagonist. This study examines the influence of anaesthetic agents on mean arterial pressure (MAP) response to a β-blocker. Cumulative dose-response curves of propranolol (non-selective), ICI 118,551 (β_2-selective) and atenolol (β_1-selective) were constructed in phentolamine-treated rats anaesthetized with urethane, pentobarbitone or halothane. I.v. injections of all three β-blockers caused dose-dependent increases in MAP in urethane-anaesthetized rats. In halothane-anaesthetized rats, propranolol and atenolol did not alter MAP while ICI 118,551 caused a small dose-dependent increase in MAP. In the presence of pentobarbitone, none of the β-blockers raised MAP. In the second series of experiments, a single i.v. bolus dose of propranolol was given in phentolamine-treated rats anaesthetized with pentobarbitone, amobarbitone, ketamine or chloralose. Propranolol did not affect MAP in rats anaesthetized with pentobarbitone, amobarbitone and chloralose but it partially reversed the hypotensive effect of phentolamine in ketamine-anaesthetized rats. In the third series, propranolol or atenolol was i.v. injected in pentobarbitone-anaesthetized rats treated with both phentolamine and adrenaline. Both propranolol and atenolol raised MAP. Our results show that anaesthetic agents differentially affect the MAP response to a β-blocker.

Paradoxical pressor responses to β-adrenoceptor antagonists have been reported in urethane-anaesthetized rats (Dasgupta 1968; Himori et al 1984). The pressor response was exaggerated in the presence of a non-selective α-adrenoceptor antagonist (Yamamoto & Sekiya 1969; Regoli 1970). The administration of either propranolol (non-selective), ICI 118,551 (erythro-(+)-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol) (β_2-selective) or atenolol (β_1-selective) into conscious rats, however, did not affect blood pressure (Tabrizchi et al 1988). After pretreatment of conscious rats with phentolamine, the injection of low doses of either propranolol, atenolol or ICI 118,551 caused similar dose-dependent increases in arterial pressure (Tabrizchi et al 1988). This suggests that pressor response to a β-adrenoceptor antagonist is not a result of the blockade of vasodilator β_2-adrenoceptors. That α-adrenoceptor blockade is essential for the pressor response to propranolol was again demonstrated in another study whereby hypotension caused by the nitrosovasodilator nitroprusside or the cholinergic agonist methacholine did not precipitate a pressor response to propranolol (Tabrizchi & Pang 1989). This suggests that the pressor response appears to be the result of a specific interaction between an α- and a β-adrenoceptor antagonist.

Paradoxical pressor responses to β-blockers have been shown to occur in patients previously given an α-adrenoceptor antagonist (Prichard & Ross 1966; Cleophas & Kauw 1988). Many studies have used anaesthetized animals to examine the mechanisms responsible for pressor response to β-blockers. We found that the β-blocker-induced pressor response is much affected by anaesthetic agents; it is present in conscious rats (Tabrizchi et al 1988; Tabrizchi & Pang 1989) and urethane-anaesthetized rats (Regoli 1970; Abdelrahman & Pang 1990) but is absent in pentobarbitone-anaesthetized rats (unpublished data). Since anaesthetic agents have variable and profound influences on the direction and magnitude of response to a β-blocker, it is the aim of this study to compare the effects of common i.v. and inhalation anaesthetic agents on pressor response to a β-blocker.

Correspondence: C. C. Y. Pang, Department of Pharmacology and Therapeutics, Faculty of Medicine, University of British Columbia, 2176 Health Sciences Mall, Vancouver, BC, V6T 1Z3 Canada.

Materials and Methods

Surgical preparation

Male Sprague-Dawley rats, 300–400 g, were anaesthetized with one of the following i.v. or inhalation anaesthetic agents: urethane (1 g kg^{-1}, i.p.), pentobarbitone (65 mg kg^{-1}, i.p.), amobarbitone (100 mg kg^{-1}, i.p.), ketamine (125 mg kg^{-1}, i.p.), chloralose (90 mg kg^{-1}, i.p.) and halothane (4% in air for induction and 1·5% in air for maintenance). The body temperature of each rat was maintained at 37°C with a heating pad connected to a thermostat (Yellow Spring Instruments, model 73A). The doses of pentobarbitone, amobarbitone, urethane and halothane were those which inhibited either eyelid, corneal or limb reflexes to painful stimuli. In most cases, some, but not all, of the reflexes tested were still present. The femoral artery and both femoral veins of the anaesthetized rats were cannulated for the measurement of mean arterial pressure (MAP) and injection of drugs, respectively.

Experimental protocol

Effects of urethane, pentobarbitone and halothane on dose-response curves to propranolol, atenolol and ICI 118,551. Rats were divided into nine groups: Groups I, II and III (n = 6 each) were anaesthetized with urethane; Groups IV (n = 5), V

(n=6) and VI (n=6) were anaesthetized with pentobarbitone; Groups VII (n=8), VIII (n=6) and IX (n=6) were anaesthetized with halothane. All rats were continuously infused with phentolamine (10^{-6} mol kg^{-1} min^{-1}). After 10 min of infusion, a dose-response curve to i.v. bolus injections of a β-adrenoceptor antagonist was constructed in each group of rats: propranolol (3×10^{-9}–$3{\cdot}84 \times 10^{-7}$ mol kg^{-1}) in Groups I, IV and VII; ICI 118,551 (2×10^{-9}–$1{\cdot}28 \times 10^{-7}$ mol kg^{-1}) in Groups II, V and VIII; atenolol (3×10^{-9}–$3{\cdot}84 \times 10^{-7}$ mol kg^{-1}) in Groups III, VI and IX. MAP readings were noted at 1 min after the injection of each dose of a β-blocker.

Effects of pentobarbitone, amobarbitone, ketamine and chloralose on i.v. bolus of propranolol. Rats were divided into four groups (n=5–6 each): Group X, XI, XII and XIII were anaesthetized with pentobarbitone, amobarbitone, ketamine and chloralose, respectively. All rats were continuously infused with phentolamine (10^{-6} mol kg^{-1} min^{-1}). Ten min after the start of phentolamine infusion, propranolol (3×10^{-7} mol kg^{-1}) was i.v. injected into each rat. MAP was noted 10 min after phentolamine infusion and 1 min after the injection of propranolol.

Effect of adrenaline on i.v. bolus propranolol and atenolol in pentobarbitone-anaesthetized rats. Two groups of pentobarbitone-anaesthetized rats (n=6 each) were used. Groups XIV and XV were given continuous i.v. infusion of adrenaline ($1{\cdot}6 \times 10^{-9}$ mol kg^{-1} min^{-1}) followed 10 min later by continuous i.v. infusion of phentolamine (10^{-6} mol kg^{-1} min^{-1}). After another 10 min, propranolol (3×10^{-7} mol kg^{-1}) and atenolol (3×10^{-7} mol kg^{-1}) were i.v. injected into Group XIV and XV, respectively. MAP was noted 10 min after adrenaline and phentolamine infusions and 1 min after the injection of a β-blocker.

Statistical analysis

All results were analysed by analysis of variance (ANOVA) followed by Duncan's multiple range test to compare group means. In all cases, $P < 0{\cdot}05$ was selected as the criterion for statistical significance.

Drugs

Drugs used included: halothane (Ayerst Lab., Montreal, Canada), α-chloralose (BDH Chemical Ltd, Poole, UK), (±)-propranolol HCl, atenolol, urethane ethyl carbamate, adrenaline and ketamine HCl (all from Sigma Chemical Co., MO, USA), sodium pentobarbitone (M.T.C. Pharmaceuticals, Ontario, Canada), phentolamine hydrochloride (CIBA Geigy, NJ, USA), ICI 118,551 (ICI, Macclesfield, UK) and amobarbitone (Eli Lilly & Co., Ontario, Canada).

(±)-Propranolol HCl, phentolamine and atenolol were dissolved in 0·9% NaCl solution (saline). ICI 118,151 was dissolved in distilled water followed by dilution with saline.

Results

Effects of urethane, pentobarbital and halothane on dose-response curves to a β-adrenoceptor antagonist

Baseline MAP (pooled value) in rats anaesthetized with pentobarbitone is significantly higher than MAP in rats anaesthetized with urethane or halothane (Table 1). Phentolamine reduced MAP in rats in Groups I to IX (Table 1). An i.v. bolus dose of propranolol, ICI 118,551 or atenolol dose-dependently increased MAP in rats anaesthetized with urethane but not pentobarbitone (Fig. 1a, b, c). In rats anaesthetized with halothane, ICI 118,551, but not propranolol or atenolol, caused a small dose-dependent increase in MAP. Maximal increase in MAP with ICI 118,551 under the influence of halothane (Group VIII) was approximately 25% of that under the influence of urethane (Group II) even when baseline MAP values before and after the infusion of phentolamine were similar in the two groups (Table 1).

Table 1. Mean arterial pressure (mean ± s.e.) before and 10 min after the infusion of phentolamine (10^{-6} mol kg^{-1} min^{-1}) in rats anaesthetized with urethane (Groups I–III), pentobarbitone (Groups IV–VI) or halothane (Groups VII–IX).

	Mean arterial pressure (mm Hg)	
	Control	*Phentolamine*
Urethane		
Group I	92 ± 7	56 ± 6[a]
Group II	84 ± 2	48 ± 6[a]
Group III	92 ± 7	47 ± 2[a]
Pooled	89 ± 3	51 ± 3[a]
Pentobarbital		
Group IV	105 ± 3	66 ± 6[a]
Group V	103 ± 7	77 ± 4[a]
Group VI	100 ± 3	80 ± 2[a]
Pooled	102 ± 2[b]	75 ± 3[a]
Halothane		
Group VII	98 ± 1	69 ± 3[a]
Group VIII	84 ± 1	47 ± 2[a]
Group IX	83 ± 3	61 ± 2[a]
Pooled	89 ± 2	63 ± 2[a]

n=5–8 per group. [a]Significantly different from control values ($P < 0{\cdot}05$). [b]Significantly different from pooled values in rats anaesthetized with urethane or halothane ($P < 0{\cdot}05$).

Effects of pentobarbitone, amobarbitone, ketamine and chloralose on i.v. bolus of propranolol

In Groups X, XI and XIII rats anaesthetized with pentobarbitone, amobarbitone or chloralose, phentolamine reduced MAP while propranolol did not produce any significant effect on MAP (Fig. 2). In Group XII rats anaesthetized with ketamine, the control MAP was higher than those under the influence of other anaesthetic agents. In these rats, phentolamine caused a greater reduction of MAP than in rats anaesthetized with pentobarbitone, amobarbitone or chloralose. The injection of propranolol partially restored MAP to a level which was lower than baseline MAP (Fig. 2).

Effect of adrenaline on i.v. bolus propranolol and atenolol in pentobarbitone-anaesthetized rats

In Groups XIV and XV, the infusion of adrenaline caused a small increase in MAP which was significant in Group XV but not in XIV. The infusion of phentolamine reduced MAP in both groups. I.v. bolus of propranolol and atenolol partially restored MAP to levels lower than MAP after the infusion of adrenaline (Fig. 3).

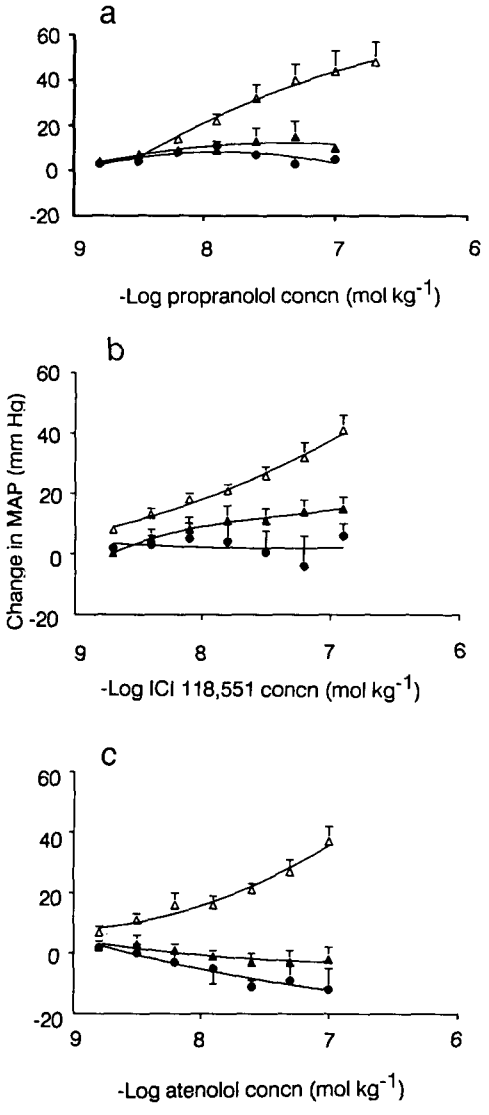

FIG. 1. Dose-response curves for the effects of propranolol, atenolol and ICI 118,551 on mean arterial pressure (MAP) in 9 groups of urethane, pentobarbitone and halothane anaesthetized rats pretreated with phentolamine. Each point represents the mean ± s.e. (n = 5–8 per group). △, Urethane; ●, pentobarbitone; ▲, halothane.

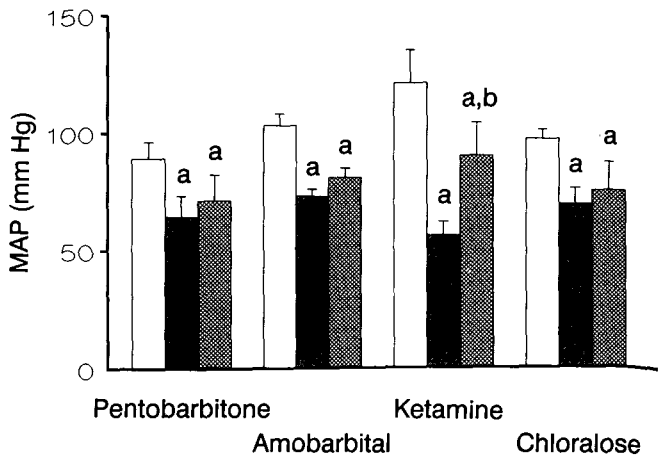

FIG. 2. Mean arterial pressure (MAP) in groups of rats anaesthetized with pentobarbitone, amobarbitone, ketamine or chloralose (n = 5–6 in each group) during control conditions (open bars), 10 min after the start of a continuous infusion of phentolamine (hatched bars) and 1 min after the injection of propranolol during the infusion of phentolamine (cross-hatched bars). [a]Significantly different from control ($P < 0.05$); [b]significantly different from phentolamine infusion ($P < 0.05$).

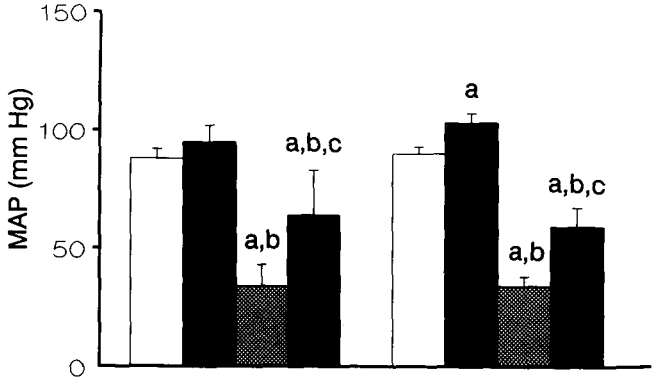

FIG. 3. Mean arterial pressure (MAP) in groups of rats anaesthetized with pentobarbitone (n = 6 in each group), during control conditions (open bars), 10 min after the start of adrenaline infusion (hatched bars), 10 min after the start of phentolamine infusion in the presence of adrenaline (cross-hatched bars) and 1 min after the injection of propranolol or atenolol during the infusions of adrenaline and phentolamine (solid bars). [a]Significantly different from control ($P < 0.05$); [b]significantly different from adrenaline ($P < 0.05$); [c]significantly different from phentolamine ($P < 0.05$).

Discussion

Pressor response to β-blockers in the presence of α-blockade has been observed in conscious (Tabrizchi et al 1988; Tabrizchi & Pang 1989) and urethane-anaesthetized rats (Abdelrahman & Pang 1990). In the present study, we examined the effects of i.v. and inhalation anaesthetic agents on the pressor response to β-blockers. In urethane-anaesthetized rats pretreated with phentolamine, i.v. bolus of propranolol, atenolol or ICI 118,551 each produced a dose-dependent increase in MAP which restored MAP to control levels before the administration of phentolamine. We have previously reported that the pressor response to propranolol in urethane-anaesthetized rats pretreated with phentolamine was primarily due to a reversal of the vasodilator effect of phentolamine (Abdelrahman & Pang 1990). It is unlikely that β_2-induced vasodilation was the mechanism responsible for pressor response to a β-blocker since it has been shown that the injections of very small doses of either the selective β_1-antagonist, atenolol, or the selective β_2-antagonist, ICI 118,551, into conscious rats caused pressor responses of similar magnitudes (Tabrizchi et al 1988).

In halothane-anaesthetized rats, phentolamine also reduced MAP. However, the subsequent injection of propranolol or atenolol did not produce a pressor response. On the other hand, ICI 118,551 caused a small dose-dependent increase in MAP. The maximum rise in MAP was 25% of that in conscious rats (Tabrizchi et al 1988; Tabrizchi & Pang 1989) and urethane-anaesthetized rats in the present study. It has been shown that phentolamine decreases MAP in halothane-anaesthetized rats by reducing cardiac output but

not total peripheral resistance (Tabrizchi & Pang 1987). It is therefore conceivable that the lack of pressor response with propranolol and atenolol in phentolamine-treated rats is related to the possible further reduction of cardiac output via the blockade of β_1-adrenoceptors. Halothane has been reported to attenuate the pressor response to phenylephrine and azepexole (Kenny et al 1990). Halothane also reduced the amplitude of oscillations produced by noradrenaline in the rabbit isolated meseneric vein and this was attributed to the inhibition of calcium release from the sarcoplasmic reticulum (Marijic et al 1990). This anaesthetic agent also reduced 5-hydroxytryptamine- and acetylcholine-induced contractility in endothelium-free porcine coronary artery and this was thought to be due to the inhibitory effect of halothane on agonist-induced inositol phosphate formation (Ozhan et al 1990). Su & Zhang (1989) showed that halothane decreased tension development in intact aortic rings due to combined effects of a depression of Ca^{2+}-induced activation of the contractile proteins and a decrease of sarcoplasmic reticulum Ca^{2+} accumulation leading to reduced Ca^{2+} release for muscle contraction. Therefore, it is possible that non-specific inhibition of Ca^{2+}-release could be responsible for the inhibition of pressor response to β-blockers.

In pentobarbitone-anaesthetized rats, all β-blockers failed to produce a pressor response. Pentobarbitone has been shown to decrease plasma catecholamine levels in rats (Farnebo et al 1979) and dogs (Zimpfer et al 1982; Baum et al 1985). Holmes & Schneider (1973) reported that pentobarbitone reduced acetylcholine-induced catecholamine release in isolated chromaffin bovine vesicles. The mechanism may involve the interruption of a link between receptor activation and catecholamine release. In order to examine whether or not catecholamines affect the pressor response to propranolol, adrenaline was infused into two additional groups of rats. The infusion of phentolamine in rats pretreated with adrenaline caused markedly greater reductions in MAP. The subsequent injections of both propranolol and atenolol partially restored MAP. Since propranolol and atenolol caused similar pressor responses, it is unlikely that the partial reversal was only a consequence of the blockade of vasodilatory β_2-adrenoceptors. These results are not in accordance with results which show that the pressor response to a β-blocker was mainly due to the blockade of vasodilating β_2-adrenoceptors (Himori & Ishimori 1988; Himori et al 1984). These results are in agreement with those of Tabrizchi & Pang (1990) which show that adrenaline is required in the antagonism by β-blockers of phentolamine-induced hypotension. Further experiments were carried out to examine if other barbiturate anaesthetic agents similarly suppress the pressor response to propranolol. The results show that propranolol also failed to produce a pressor response in rats anaesthetized with amobarbitone.

Under the influence of ketamine, propranolol partially reversed the hypotensive effect of phentolamine. Ketamine is known to stimulate the cardiovascular system by its central sympathomimetic actions and the inhibition of intraneuronal and extraneuronal catecholamine uptake (Riou et al 1989). This may explain why control MAP was higher in rats anaesthetized with ketamine than in those with the other anaesthetic agents. It has been shown in in-vivo studies that, in the absence of autonomic control, ketamine directly depresses the myocardium (Schwartz & Horwitz 1975). Additionally, ketamine has been shown to exert an intrinsic depressant effect on the ventricle contractile apparatus (Cook et al 1990). It is therefore possible that following α- and β-adrenoceptor blockade, the direct myocardial depressant effect of ketamine partially abolished the pressor response to propranolol. In in-vitro studies, ketamine, in doses relevant to those used in surgical induction, inhibited the development of spontaneous mechanical activity and lowered baseline tension of rat aortae and portal veins. In addition, ketamine attenuated noradrenaline-, KCl-, angiotensin II- and vasopressin-induced contractions of rat aortic strips (Altura et al 1980). The relaxant effect of ketamine is probably due to a decrease of Ca^{2+}-influx through the plasma membrane or an interference with the process of signal transduction between receptor occupation on the plasma membrane and Ca^{2+}-release from intracellular stores (Kanmura et al 1989). Therefore, it is also possible that ketamine attenuated the pressor response to β-blockers by its direct relaxant effect.

In chloralose-anaesthesia, pressor response to a β-blocker was completely abolished. Chloralose had a profound negative inotropic effect on the dog heart-lung preparation (Bass & Buckley 1966). Charney et al (1970) showed that chloralose anaesthesia in dogs was associated with a transient increase in cardiac output which was abolished by α- and β-blockade. The intrinsic depressant effect of chloralose, like that of ketamine, may have been normally masked by the sympathomimetic effects of the anaesthetic. However, following α- and β-adrenoceptor blockade, the myocardial depressant effect of chloralose may have been unmasked resulting in the abolition of pressor response to a β-adrenoceptor antagonist.

In summary, our results show that anaesthetic agents have varying effects on the MAP response to a β-blocker in phentolamine-treated rats. This variability ranges from a marked pressor response resulting in the reversal of the hypotensive effect of phentolamine in conscious rats and rats anaesthetized with urethane, to attenuated pressor response with halothane and ketamine and, complete abolition of pressor response with halothane, pentobarbitone, amobarbitone and chloralose. Due to the possibility of a large variability in response to a vasoactive drug under the influence of anaesthetic agents, great caution must be taken when interpreting results obtained from anaesthetized animals.

Acknowledgements

This work was supported by the Medical Research Council of Canada. A. Abdelrahman is the recipient of a University of British Columbia graduate fellowship. The authors would like to thank ICI PLC UK for the supply of ICI 118,551.

References

Abdelrahman, A., Pang, C. C. Y. (1990) Haemodynamic changes that accompany the pressor response to propranolol in urethane anaesthetized rats subjected to α-blockade. Pharmacology 40: 293–300

Altura, B. M., Altura, B. T., Carella, A. (1980) Effects of ketamine

on vascular smooth muscle function. Br. J. Pharmacol. 70: 257–267

Bass, B. G., Buckley, N. M. (1966) Chloralose anesthesia in the dog: a study of drug actions and analytical methodology. Am. J. Physiol. 210: 854–862

Baum, D., Halter, J. B., Taborsky G. J., Porte, D. (1985) Pentobarbital effects on plasma catecholamines: temperature, heart rate, and blood pressure. Ibid. 248: E95–E100

Charney, A. N., Bass, B. G., Buckley, N. M. (1970) Cardiovascular effects of chloralose in catecholamine-depleted or receptor-blocked dogs. Arch. Int. Pharmacodyn. 185: 397–405

Cook, D. J., Carton, E. G., Housmans, P. R. (1990) Direct and indirect effects of ketamine on mammalian ventricular myocardium. Anesthesiology 73: A617

Cleophas, T. J. M., Kauw, F. H. W. (1988) Pressor responses from noncardioselective β-blockers. Angiology 39: 587–596

Dasgupta, N. K. (1968) On the mechanism of the pressor response due to propranolol. Br. J. Pharmacol. 34: 200P–201P

Farnebo, L., Hallman, H., Hamberger, B., Jonsson, G. (1979) Catecholamines and hemorrhagic shock in awake and anesthetized rats. Circ. Shock 6: 109–118

Himori, N., Ishimori, T. (1988) Different responses to β-adrenoceptor blocking drugs of the blood pressure and heart rate in the urethane-anaesthetized dog and rat. Jap. J. Pharmacol. 47: 71–80

Himori, N., Ishimori, T., Shiratsuchi, K., Tsuneda, K., Izumi, A. (1984) Role of β_2-adrenoceptor blockade and circulating adrenaline level for the pressor response to β-adrenoceptor blocking drugs in rats. Naunyn Schmiedebergs Arch. Pharmacol. 325: 314–319

Holmes, J. C., Schneider, F. H. (1973) Pentobarbitone inhibition of catecholamine secretion. Br. J. Pharmacol. 49: 205–213

Kanmura, Y., Yoshitake, J., Casteels, R. (1989) Ketamine-induced relaxation in intact and skinned smooth muscles of the rabbit ear artery. Ibid. 97: 591–597

Kenny, D., Pelc, L.R., Brooks, H. L., Kampine, J. P., Schmeling, W. T., Warltier, D. C. (1990) Calcium channel modulation of α_1- and α_2-adrenergic pressor responses in conscious and anaesthetized dogs. Anesthesiology 72: 874–881

Marijic, J., Madden, J. A., Kampine, J. P., Bosnjak, Z. J. (1990) The effect of halothane on norepinephrine responsiveness in rabbit small mesenteric veins. Ibid. 73: 479–484

Ozhan, M., Sill, J. C., Katusic, Z., Nelson, R., Iaizzo, P. (1990) Isoflurane, halothane and second messenger pathways in isolated pig coronary arteries. Ibid. 73: A554

Prichard, B. N. C., Ross, E. J. (1966) Use of propranolol in conjunction with α-receptor blocking drugs in pheochromocytoma. Am. J. Cardiol. 18: 394–398

Regoli, D. (1970) Pressor action of beta blocking agents in rats. Can. J. Physiol. Pharmacol. 48: 481–489

Riou, B., Lecarpentier, Y., Viars, P. (1989) Inotropic effect of ketamine on rat cardiac papillary muscle. Anesthesiology 71: 116–125

Schwartz, D. A., Horwitz, L. (1975) Effects of ketamine on left ventricular performance. J. Pharmacol. Exp. Ther. 194: 410–414

Su, J. Y., Zhang, C. (1989) Intracellular mechanisms of halothane's effect on isolated aortic strips of the rabbit. Anesthesiology 71: 409–417

Tabrizchi, R., Pang, C. C. Y. (1987) Comparative effects of rauwolscine, prazosin and phentolamine on blood pressure and cardiac output in anaesthetized rats. Can. J. Physiol. Pharmacol. 65: 1421–1427

Tabrizchi, R., Pang, C. C. Y. (1989) Propranolol antagonizes hypotension induced by α-blockers but not by sodium nitroprusside or methacholine. Ibid. 67: 83–87

Tabrizchi, R., Pang, C. C. Y. (1990) Adrenalectomy abolishes antagonism of α-adrenoceptor-mediated hypotension by a β-blocker in conscious rats. Br. J. Pharmacol. 101: 358–362

Tabrizchi, R., King, K. A., Pang, C. C. Y. (1988) Pressor response to β_1- and β_2-blockers in conscious rats treated with phentolamine. Pharmacology 37: 385–393

Yamamoto, J., Sekiya, A. (1969) On the pressor action of propranolol in the rat. Arch. Int. Pharmacodyn. 179: 372–380

Zimpfer, M., Manders, W. T., Barger, A. C., Vatner, S. F. (1982) Pentobarbital alters compensatory neural and humoral mechanisms in response to hemorrhage. Am. J. Physiol. 243: H713–H721