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Cardiovascular actions of a new selective postjunctional α-adrenoceptor antagonist, SK&F 104856, in normotensive and hypertensive dogs

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1 SK&F 104856 (2-vinyl-7-chloro-3,4,5,6-tetrahydro-4-methylthieno[4,3,2ef][3]benzazepine) is a novel postjunctional α_1- and α_2-adrenoceptor antagonist.

2 SK&F 104856 as well as prazosin and SK&F 86466 reduced blood pressure in the anaesthetized normotensive dog.

3 SK&F 86466 and rauwolscine but not SK&F 104856 or prazosin, produced a marked increase in myocardial contractility which corresponds with their ability to block prejunctional α_2-adrenoceptors.

4 Intravenous or oral administration of SK&F 104856 resulted in dose-dependent antihypertensive responses in 1-kidney, 1-clip (1-K, 1-C) Goldblatt hypertensive dogs with baseline blood pressure of approximately 140 mmHg. At 0.1 and 1 mg kg^{-1}, i.v., mean arterial blood pressure fell by 11 ± 5 and 23 ± 5 mmHg, respectively. At 3 and 10 mg kg^{-1}, p.o., blood pressure fell by 9 ± 3 and 22 ± 5 mmHg, respectively. At 10 mg kg^{-1}, p.o., the antihypertensive effect of SK&F 104856 was still evident at 4 h.

5 The data indicate that SK&F 104856 shows selectivity *in vivo* for postjunctional versus prejunctional α-adrenoceptors and is a potent and long-acting antihypertensive agent in 1-K, 1-C Goldblatt hypertensive dogs.

Keywords: Hypertension; α-adrenoceptors; normotensive and hypertensive dogs; SK&F 104856

Introduction

SK&F 104856 (2-vinyl-7-chloro-3,4,5,6-tetrahydro-4- methylthieno[4,3,2ef][3]benzazapine) is a novel α-adrenoceptor antagonist having pharmacological properties distinct from both non-selective antagonists such as phentolamine and selective α_1-adrenoceptor antagonists such as prazosin. SK&F 104856 produces competitive blockage of both α_1-adrenoceptors and α_2-adrenoceptors located on isolated blood vessels and will inhibit the binding of both [^{3}H]-rauwolscine and [^{3}H]-prazosin to rat cortical homogenates (Hieble *et al.*, 1991). However, in several field-stimulated preparations, SK&F 104856 neither enhances neurotransmitter release nor inhibits the neuroinhibitory action of an exogenous α_2-adrenoceptor agonist (Hieble *et al.*, 1991). Hence, SK&F 104856 appears to have the ability to block vascular α-adrenoceptors, both α_1 and α_2 , without interfering with the neuronal α_2-adrenoceptor responsible for feedback control of neurotransmitter release.

There is evidence for a contribution of both α_1- and α_2-adrenoceptor activation to the maintenance of elevated blood pressure in hypertension. In normotensive rats, selective α_1-adrenoceptor blockade with prazosin, but not selective α_2-adrenoceptor blockade with rauwolscine, would lower blood pressure. However, in either DOCA-salt hypertensive or spontaneously hypertensive rats, rauwolscine will reduce blood pressure when given alone, and produce an additional antihypertensive effect following a maximally effective dose of prazosin (McCafferty *et al.*, 1982). Other investigators have observed an additional blood pressure reduction by rauwolscine in prazosin-treated spontaneously hypertensive rats (Sawyer *et al.*, 1985). Functional vasoconstrictor responses mediated by vascular α_2-adrenoceptors have been demonstrated in both normotensive and hypertensive human subjects (Bolli *et al.*, 1984; Jie *et al.*, 1986; Brown, 1989), and may be activated to a greater extent in the hypertensive state (Bolli *et al.*, 1984).

Hence, the ability of an agent, such as SK&F 104856, to block both α_1-adrenoceptors and α_2-adrenoceptors on vascular smooth muscle while, like prazosin, preserving prejunctional α_2-adrenoceptor-mediated control of transmitter release, may be advantageous in the treatment of conditions associated with elevated vascular resistance. In the present study, we characterize the *in vivo* effects of SK&F 104856 in the dog, evaluating antihypertensive efficacy in the conscious 1-kidney, 1-clip Goldblatt preparation, and using myocardial contractility in the anaesthetized normotensive animal as an index of interaction with prejunctional α_2-adrenoceptors.

Methods

All experimental procedures were approved by the Institutional Animal Care and Use Committee and were in accordance with National Institutes of Health guidelines for the care and use of animals.

Haemodynamic studies in the anaesthetized dog

Myocardial contractility Adult mongrel dogs of either sex (12–20kg) were anaesthetized with sodium pentobarbitone (50 mg kg^{-1}, i.p.) and prepared as described previously (Hieble *et al.*, 1987). Briefly, a tracheotomy was performed and the animal was connected to a large animal respirator, delivering a tidal volume of 15–20 ml kg^{-1} at 16 cycles min^{-1}. The right femoral vein and artery were isolated and cannulated. A left thoracotomy was performed at the fourth intercostal space. The pericardial sac was opened, and a wide bore catheter was inserted into the left ventricle near the apex to measure left ventricular pressure. The left ventricular pressure signal was used to obtain dP/dt. After allowing at least 30 min post surgery to allow stabilization of haemodynamic parameters, α-adrenoceptor antagonists were

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infused for 10 min. Blood pressure, heart rate and dP/dt were monitored continuously during infusion and for 30 min post infusion.

Vascular α-adrenoceptor responsiveness Dogs were anaesthetized as above and the right femoral artery and vein were cannulated for the measurement of blood pressure and the administration of fluids and supplemental anaesthesia, respectively. The left femoral vein was cannulated for the intravenous infusion of SK&F 104856. In order to measure the interaction of SK&F 104856 with vascular α_1-adrenoceptors, methoxamine (3 doses, 5 min intervals between doses) was administered before and during infusion of SK&F 104856. Following initiation of antagonist infusion, a 30 min stabilization period was allowed before repeating the methoxamine challenge. In experiments to evaluate blockade of vascular postjunctional α_2-adrenoceptors, the left femoral artery was isolated and femoral arterial blood flow was measured with a Carolina Medical Electronics flow probe. A needle catheter was inserted into the femoral artery distal to the flow probe for the intraarterial administration of the α_1-adrenoceptor agonist, B-HT 933 (2-amino-6-ethyl-5,6,7,8-tetrahydro-4H-oxazolo[4,5-d]azepine). Following a 30 min stabilization period, increasing doses of B-HT 933 were injected into the femoral artery, and the increase in femoral vascular resistance was measured as the change in mean arterial pressure/the change in femoral arterial blood flow. When femoral vascular resistance had returned to control levels, SK&F 104856 was infused at 100 $\mu g\,kg^{-1}\,min^{-1}$, i.v. and the dose-response curve to B-HT 933 was repeated.

Conscious hypertensive dogs

Surgical procedure Animals were appropriately premedicated; anaesthesia was induced with sodium biotol and maintained with isofluorane. With use of standard aseptic techniques and via a flank incision, a right uninephrectomy was performed. Approximately 6 weeks later and via a midline incision, a Goldblatt clamp (Braintree Scientific) was placed on the left renal artery. The clamp was constricted to reduce blood flow (measured acutely during the surgery with a flow meter) by approximately 50%. Dogs were not studied for at least 4 weeks following clamping of the renal artery.

By use of the same incision site and creation of a subcutaneous pocket, the access portion of a Vascular-Access-Port (VAP; Norfolk Medical Products, Inc.) was sutured (000-silk) to the underlying muscle in the area of the paralumbar fossa. The catheter end of the VAP was tunnelled to the area of the left femoral triangle. A second incision was made and the catheter inserted in the femoral artery to a length of approximately 12 cm and secured with 0-silk. The patency of the VAP was maintained by flushing weekly with saline and locking with a heparinized glucose solution (50% glucose-500u ml^{-1} of heparin). Animals were routinely given a broad-spectrum antibiotic for 5 days after surgery.

Experimental protocol Dogs were fasted for 18 h with free access to water before study. The dogs were placed in a sling and the glucose/heparin lock of the VAP was evacuated and the VAP connected to a Gould P23 XL pressure transducer via an infusion set. MABP and heart rate (determined from the arterial pulse) were recorded on a Gilson duograph. When i.v. administration of drugs was performed, a catheter was placed in the saphenous vein.

At least 60 min was allowed for MABP and heart rate to stabilize and then a mean of 4 values were recorded at 10 min intervals before drug administration. This was considered the control value. SK&F 104856 was administered either intravenously at 0.1 or 1 $mg\,kg^{-1}$, i.v. or p.o. at 3 or 10 $mg\,kg^{-1}$ (in a gelatin capsule). Blood pressure and heart rate were monitored over the next 4 h. Four animals were used in each group and a period of at least 2 weeks was allowed between each experiment.

Data analyses

All data are reported as means ± s.e. Statistical analysis was performed by analysis of variance for repeated measures.

Results

Intravenous infusion of either prazosin (10 $\mu g\,kg^{-1}\,min^{-1}$), SK&F 86466 (100 $\mu g\,kg^{-1}\,min^{-1}$) or SK&F 104856 (100 or 200 $\mu g\,kg^{-1}\,min^{-1}$) reduced blood pressure in the anaesthetized, normotensive dog. The blood pressure reduction produced by SK&F 104856 appeared to be dose-related. In contrast, rauwolscine (10 $\mu g\,kg^{-1}\,min^{-1}$) produced a slight increase in blood pressure. All drugs produced a small increase in heart rate (<15% increase, data not shown). However, SK&F 86466 and rauwolscine, but not prazosin or SK&F 104856, produced a marked increase in myocardial contractility, as measured by ventricular dP/dt (Figure 1).

Infusion of SK&F 104856 at 100 $\mu g\,kg^{-1}\,min^{-1}$ was shown to block both the pressor response to α_1-adrenoceptor activation by methoxamine and the ability of the selective α_2-adrenoceptor agonist, B-HT 933, to increase femoral vascular resistance (Table 1), demonstrating *in vivo* blockade of both vascular α-adrenoceptor subtypes at this dose. Increases in hind limb vascular resistance were used as an index of α_2-adrenoceptor activation, rather than systemic pressor responses, since the pressor dose-response curve to selective α_2-adrenoceptor agonists in the anaesthetized dog is shallow and has a low maximum response.

The ability of SK&F 104856 to lower blood pressure in conscious dogs in which hypertension had been induced by renal artery clamping was studied. Baseline blood pressure in normotensive animals prior to placing the Goldblatt clamp on the renal artery was between 100–110 mmHg. Four weeks following placement of the clip, MABP averaged approximately 140 mmHg. Intravenous administration of SK&F 104856 resulted in a rapid, dose-dependent decrease in mean

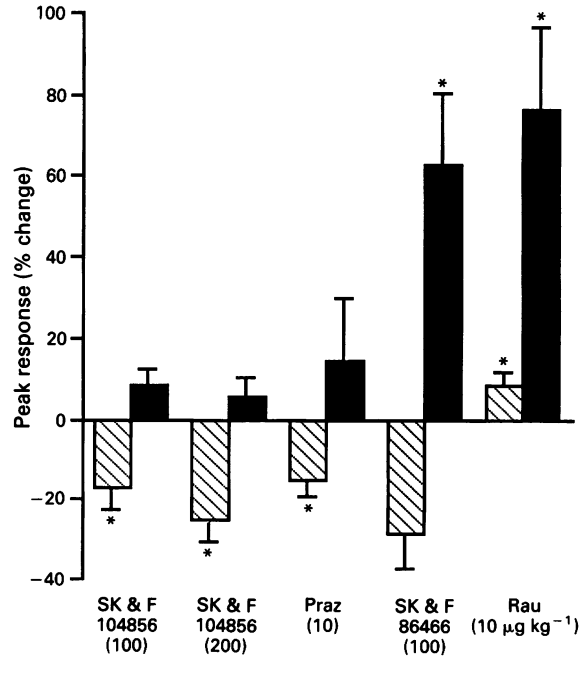

Figure 1 Comparison of the effects of various α-adrenoceptor antagonists on mean arterial blood pressure (MAP, hatched columns) and myocardial contractility (dP/dt, solid columns) in the anaesthetized dog. Praz, prazosin; Raw, rauwolscine $*P<0.05$ ($n=4$).

Table 1 Blockade of postjunctional α_1-adrenoceptors and α_2-adrenoceptors by SK&F 104856 in the anaesthetized dog

Agonist dose ($\mu g\ kg^{-1}$)	α_1[a] *Control*	*SK&F 104856*[c]	α_2[b] *Control*	*SK&F 104856*[c]
1			0.2 ± 0.1	0
3	5.8 ± 2.8	0	0.9 ± 0.2	0.1 ± 0.1
10	7.8 ± 4.8	0	1.5 ± 0.2	0.2 ± 0.1
30	39.3 ± 11.1	6.7 ± 4.4	3.7 ± 0.2	0.6 ± 0.2

[a]Blockade of methoxamine-induced increases in diastolic blood pressure; agonist administered intravenously. Responses in mmHg.
[b]Blockade of B-HT 933-induced increases in vascular resistance in femoral arterial bed; agonist administered intra-arterially. Responses in $mmHg\ ml^{-1}\ min^{-1}$.
[c]SK&F 104856 administered intravenously at $0.1\ mg\ kg^{-1}\ min^{-1}$ during repeat challenge.

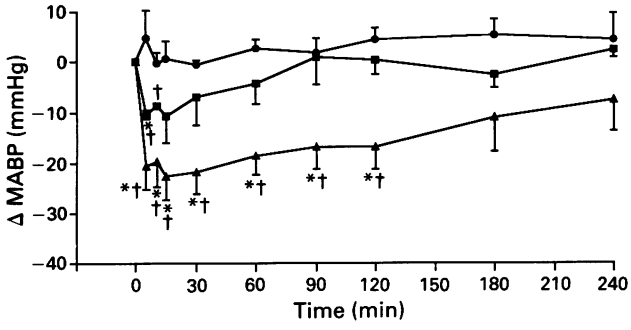

Figure 2 Time course of the effect of i.v. administration of SK&F 104856 on mean arterial blood pressure (MABP) in hypertensive dogs. Control MABP in dogs treated with vehicle (●), $0.1\ mg\ kg^{-1}$ SK&F 104856 (■) or $1\ mg\ kg^{-1}$ SK&F 104856 (▲) were 143 ± 11, 140 ± 10 and 138 ± 6 mmHg, respectively. *$P<0.05$ versus time 0; †$P<0.05$ versus vehicle.

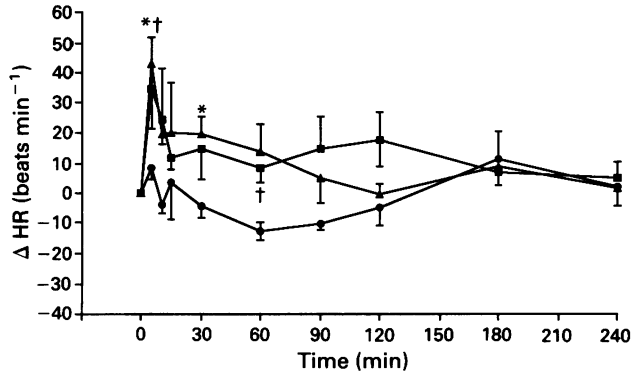

Figure 3 Time course of the effect of i.v. administration of SK&F 104856 on heart rate (HR) in hypertensive dogs. Control HR in dogs treated with vehicle (●), $0.1\ mg\ kg^{-1}$ SK&F 104856 (■) or $1\ mg\ kg^{-1}$ SK&F 104856 (▲) were 80 ± 3, 75 ± 4 and 81 ± 7 beats min^{-1}, respectively. *$P<0.05$ versus time 0; †$P<0.05$ versus vehicle.

arterial blood pressure (Figure 2). At $0.1\ mg\ kg^{-1}$, i.v. blood pressure decreased by approximately 10 mmHg, but the response was short-lived. At $1\ mg\ kg^{-1}$, i.v. blood pressure fell by 23 ± 5mmHg, and the antihypertensive response was maintained for at least 2 h (Figure 2). There was a significant reflex tachycardia associated with the initial drop in blood pressure, with both doses of SK&F 104856 increasing heart rate by approximately 40 beats min^{-1} (Figure 3); however, this response was not maintained. Thus, heart rate had returned to control levels at a time when MABP was still significantly reduced (Figures 2 and 3).

Oral administration of SK&F 104856 at $3\ mg\ kg^{-1}$ had relatively little effect on mean arterial blood pressure. However, at $10\ mg\ kg^{-1}$, blood pressure was reduced by 22 ± 5 mmHg, and this was maintained for the duration of the experiment (Figure 4). Oral administration of SK&F 104856 resulted in a slow onset of the antihypertensive action, with blood pressure reaching a minimum at 90 min. This was different from that observed after intravenous administration when blood pressure fell immediately (Figure 2). There was a small but significant increase in heart rate associated with oral administration of the higher dose of SK&F 104856 (Figure 5). This increase in heart rate paralleled, for the most part, the reduction in blood pressure.

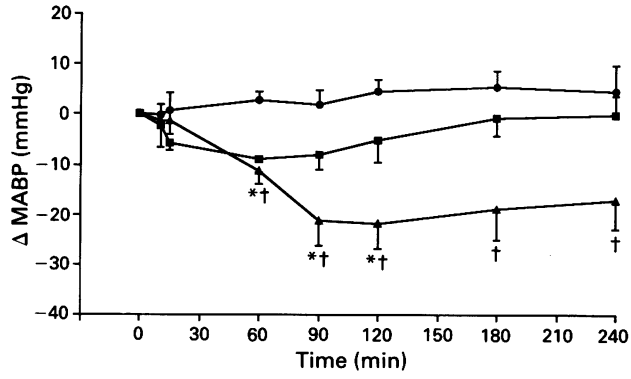

Figure 4 Time course of the effect of oral administration of SK&F 104856 on mean arterial blood pressure in hypertensive dogs. Control MABP in dogs treated with vehicle (●), $3\ mg\ kg^{-1}$ SK&F 104856 (■) or $10\ mg\ kg^{-1}$ SK&F 104856 (▲) were 143 ± 11, 142 ± 9 and 136 ± 5 mmHg, respectively. *$P<0.05$ versus time 0; †$P<0.05$ versus vehicle.

Discussion

SK&F 104856 can be considered to be structurally derived from the 3-benzazepine α-adrenoceptor antagonists, SK&F 86466 (Hieble *et al.*, 1986) and SK&F 104078 (Hieble *et al.*, 1988b). As observed with SK&F 104078, but not SK&F 86466, SK&F 104856 can discriminate between α_2-adrenoceptor populations. Based on the current observations, the *in vitro* selectivity for vascular α_2-adrenoceptors of canine and human saphenous vein, *vis-a-vis* neuronal α_2-adrenoceptors of human saphenous vein or guinea-pig atrium, can be extended to an *in vivo* preparation.

Rauwolscine and SK&F 86466, compounds of diverse chemical structure showing potent *in vitro* antagonist activity at prejunctional α_2-adrenoceptors of the guinea-pig atrium, have been shown to increase ventricular dP/dt, as assessed by studies in the anaesthetized dog. The doses required to produce maximal cardiac stimulation appear to correspond with *in vitro* α_2-adrenoceptor antagonist potency at the prejunctional receptor, with rauwolscine being 3–10 times more potent than SK&F 86466. However, in contrast, the maximal degree of inotropic stimulation produced at a given infusion

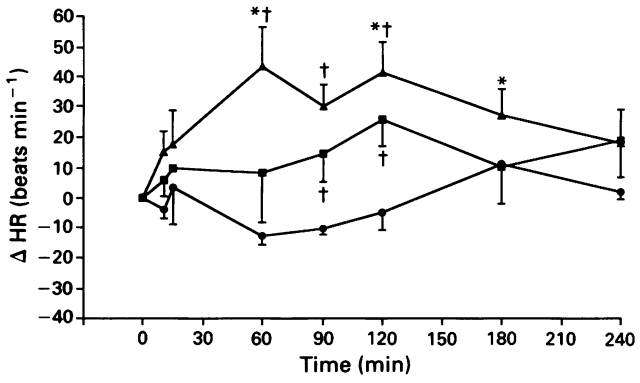

Figure 5 Time course of the effect of oral administration of SK&F 104856 on heart rate in hypertensive dogs. Control HR in dogs treated with vehicle (●), 3 mg kg^{-1} SK&F 104856 (■) or 10 mg kg^{-1} SK&F 104856 (▲) were 80 ± 3, 84 ± 11 and 75 ± 5 beats min^{-1}, respectively. *$P<0.05$ versus time 0; †$P<0.05$ versus vehicle.

rate of rauwolscine and SK&F 86466 is approximately equal (Table 2). Prazosin and SK&F 104856, which have a very low *in vitro* affinity ($K_b>1$ μM) for prejunctional α_2-adrenoceptors, produce no significant effect on contractility in the anaesthetized dog (Table 2). Our results are compatible with those observed in a similar canine preparation with two other antagonists, yohimbine and WY26392 (Paciorek & Shepperson, 1985). It is likely that the increase in dP/dt results from an enhancement in neurotransmitter release from cardiac sympathetic terminals, producing an activation of ventricular β-adrenoceptors. This is supported by the ability of propranolol to produce complete blockade of the inotropic effect of rauwolscine in this model (Hieble *et al.*, 1988a). It is interesting to note that the effects of the α_2-adrenoceptor antagonists on dP/dt, both in this study and in that described by Paciorek & Shepperson (1985), are much more dramatic than their effects on heart rate, perhaps reflecting vagally mediated compensatory mechanisms to control heart rate.

Studies in conscious hypertensive dogs show that the α-adrenoceptor blockade produced by SK&F 104856 results in a decrease in blood pressure. SK&F 104078, which shows an *in vitro* α-adrenoceptor antagonist profile similar to SK&F 104856, is not active orally, due to degradation by stomach acid (Hieble *et al.*, 1990). In contrast, SK&F 104856 shows antihypertensive activity by both oral and intravenous routes (Figures 2 and 4). Assuming we can extrapolate the data from the anaesthetized to the conscious dog, which we believe is reasonable, the inability of SK&F 104856 to elevate myocardial contractility in the anaesthetized dog indicates that its antihypertensive effect in the conscious dog might not be accompanied by an increase in plasma catecholamine levels. Plasma catecholamines were not measured in the present study since it is difficult to obtain consistent data from a conscious dog; however, studies in anaesthetized spontaneously hypertensive rats show that SK&F 104856 does not produce a statistically significant elevation of plasma noradrenaline at an effective antihypertensive dose (Sauermelch *et al.*, 1991). The effects of SK&F 104856 in this model were similar to prazosin, and in contrast to the 3–4 fold elevation in plasma noradrenaline produced by an equieffective antihypertensive dose of SK&F 86466.

Although SK&F 104856 has a haemodynamic profile in the anaesthetized instrumented dog that is similar to prazosin, the potent antagonist activity of SK&F 104856 at vascular α_2-adrenoceptors, both *in vitro* and *in vivo*, is likely to contribute to its haemodynamic effects. Studies in hypertensive rats suggest a contribution of both α_1-adrenoceptors and α_2-adrenoceptors to the maintenance of vascular tone (McCafferty *et al.*, 1982; Sawyer *et al.*, 1985), but such a contribution has not yet been established in canine models of hypertension. Nevertheless, α_2-adrenoceptors are known to play an important role in specific vascular beds.

Studies in rats (Willette *et al.*, 1991), cats (Koss *et al.*, 1991) and man (Brown, 1989) have shown an important role of the vascular α_2-adrenoceptor in the control of cutaneous blood flow. In the rat, SK&F 104856, but not prazosin, can increase flow in the cutaneous vascular bed (Sauermelch *et al.*, 1991). Since the vascular α_2-adrenoceptor makes an important contribution to coronary vascular resistance in the dog (Kopia *et al.*, 1986; Hieble *et al.*, 1988a), the addition of vascular α_2-adrenoceptor blockade may be advantageous in the treatment of hypertension with concomitant coronary artery disease.

An agent such as SK&F 104856, blocking both α_1-adrenoceptors and α_2-adrenoceptors on the vasculature, may have advantages over a selective α_1-adrenoceptor antagonist such as prazosin in the treatment of congestive heart failure. The development of tolerance to the beneficial haemodynamic effects of prazosin in heart failure patients has been postulated to result from an increased contribution of an α_2-adrenoceptor-mediated vasoconstrictor effect of the high levels of plasma catecholamines associated with heart failure (Smyth *et al.*, 1986). Furthermore, elevated pulmonary vascular tone is a clinical feature of heart failure, and studies in both dogs (Shebuski *et al.*, 1986) and cats (Hyman & Kadowitz, 1985) have shown an enhanced sensitivity to α_2-adrenoceptor-induced increases in pulmonary vascular tone under conditions where active tone was elevated. The high density of postjunctional α_2-adrenoceptor in the venous system also supports utility of a mixed antagonist such as

Table 2 Correlation of haemodynamic effects with prejunctional α_2-adrenoceptor blockade *in vitro*

Antagonist	*Postjunctional*[a] α_2K_B(nM)	*Prejunctional*[b] α_2K_B(nM)[a]	*Dose*[c] (mg kg^{-1})	dP/dt[d]
Rauwolscine	1*	4.5*	0.10	57 ± 18††
SK&F 86466	42*	17*	0.80	63 ± 18†
Prazosin	>500*	>1000*	0.1	15 ± 15†
SK&F 104856	29**	>3000**	2.0	6 ± 5

*Daly *et al.* (1988)
**Hieble *et al.* (1991)
† Valocik & Blumberg (1983)
†† Hieble *et al.* (1988a)
[a]Blockade of B-HT 920-induced contraction in canine saphenous vein.
[b]Blockade of B-HT 920-induced inhibition of neurotransmission in guinea-pig atrium.
[c]Dose required to produce maximum effect on dP/dT. Drugs infused intravenously at a rate of 0.01 mg kg^{-1}min^{-1} (rauwolscine and prazosin) or 0.1 mg kg^{-1}min^{-1} (SK&F 86466 and SK&F 104856) over a 10 min interval.
[d]Maximum increase in left ventricular dP/dT achieved.

SK&F 104856 in congestive heart failure, since cardiac preload would be expected to be reduced more effectively as a result of the addition of vascular α_2-adrenoceptor blockade.

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