***In vivo* demonstration of H₃-histaminergic inhibition of cardiac sympathetic stimulation by R- α -methyl-histamine and its prodrug BP 2.94 in the dog**

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1 The aim of this study was to investigate whether histamine H₃-receptor agonists could inhibit the effects of cardiac sympathetic nerve stimulation in the dog.

2 Catecholamine release by the heart and the associated variation of haemodynamic parameters were measured after electrical stimulation of the right cardiac sympathetic nerves (1–4 Hz, 10 V, 10 ms) in the anaesthetized dog treated with R- α -methyl-histamine (R-HA) and its prodrug BP 2.94 (BP).

3 Cardiac sympathetic stimulation induced a noradrenaline release into the coronary sinus along with a tachycardia and an increase in left ventricular pressure and contractility without changes in mean arterial pressure. Intravenous administration of H₃-receptor agonists significantly decreased noradrenaline release by the heart (R-HA at 2 μ mol kg⁻¹ h⁻¹: +77 $\pm$ 25 vs +405 $\pm$ 82; BP 2.94 at 1 mg kg⁻¹: +12 $\pm$ 11 vs +330 $\pm$ 100 pg ml⁻¹ in control conditions, $P \leq 0.05$), and increases in heart rate (R-HA at 2 μ mol kg⁻¹ h⁻¹: +26 $\pm$ 8 vs +65 $\pm$ 10 and BP 2.94 at 1 mg kg⁻¹: +30 $\pm$ 8 vs 75 $\pm$ 6 beats min⁻¹, in control conditions $P \leq 0.05$), left ventricular pressure, and contractility. Treatment with SC 359 (1 mg kg⁻¹) a selective H₃-antagonist, reversed the effects of H₃-receptor agonists. Treatment with R-HA at 2 μ mol kg⁻¹ h⁻¹ and BP 2.94 at 1 mg kg⁻¹ tended to decrease, while that with SC 359 significantly increased basal heart rate (from 111 $\pm$ 3 to 130 $\pm$ 5 beats min⁻¹, $P \leq 0.001$).

4 Functional H₃-receptors are present on sympathetic nerve endings in the dog heart. Their stimulation by R- α -methyl-histamine or BP 2.94 can inhibit noradrenaline release by the heart and its associated haemodynamic effects.

Keywords: H₃-receptors; R- α -methyl-histamine; BP 2.94; catecholamines; cardiac sympathetic nerves; dog

Abbreviations: BP, BP 2.94; CTL, Control; HR, Heart rate; R-HA, R- α -methyl-histamine; SC, SC 359

Introduction

H₃-receptors are presynaptic autoreceptors present on histaminergic nerve endings. Their stimulation is responsible for the inhibition of histamine release (Arrang *et al.*, 1983) and synthesis (Arrang *et al.*, 1987). H₃-receptors are also present on non histaminergic nerves such as serotonergic, cholinergic or adrenergic nerves in the central nervous system (Stark *et al.*, 1989) and on postganglionic sympathetic neurones (Ishikawa & Sperelakis, 1987; Imamura *et al.*, 1995) where they inhibit neuromediator release. R- α -methyl-histamine is a full agonist displaying a 15 fold higher potency than histamine at H₃-receptors and negligible potency at other receptor subtypes (Arrang *et al.*, 1987). In view of the actions of R- α -methyl-histamine, it was considered that H₃-receptor agonists display a potential therapeutic value in several fields such as migraine or inflammation (Göthert *et al.*, 1995). However, the efficacy of R- α -methyl-histamine in man is limited, as a consequence of its rapid metabolism (Rouleau *et al.*, 1997).

BP 2.94 ((R)-(–)-2-[N-[1-(1H-imidazol-4-yl)-2-propyl]-(iminophenylmethyl)]phenol) an azomethine derivative, is a stable prodrug of R- α -methyl-histamine, able to slowly release the bioactive compound, thus preventing its early metabolic degradation (Rouleau *et al.*, 1997). BP 2.94 has been shown to present antinociceptive and anti-inflammatory properties

attributable to an inhibition of tachykinin release (Rouleau *et al.*, 1997).

Since R- α -methyl-histamine attenuates the chronotropic and inotropic response to stimulation of sympathetic nerve endings in isolated guinea-pig atrial preparations by inhibiting noradrenaline release (Endou *et al.*, 1994; Imamura *et al.*, 1995), we questioned whether H₃-receptor agonists could modulate cardiac sympathetic activity *in vivo*. Therefore, the purpose of this study was to evaluate the effects of R- α -methyl-histamine and BP 2.94 on haemodynamic response and noradrenaline release induced by cardiac sympathetic nerve stimulation in the anaesthetized dog.

Methods

Animal preparation

This investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (N.I.H. Publication No. 85-23, revised 1985).

Seventeen Beagle dogs (12–20 kg) were anaesthetized with sodium pentobarbital (30 mg kg⁻¹, i.v.) and α -chloralose (80 mg kg⁻¹ followed by 10 mg kg⁻¹ h⁻¹). Positive pressure respiration with room air was maintained by a pump (Roche-Kontron 3100S) connected to an endotracheal tube. The right

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femoral vein and artery were cannulated with polyethylene catheters for drug injection and arterial pressure measurement using pressure transducers (Baxter 33-260, Healthcare Corp. U.K.). A catheter was introduced into the jugular vein and positioned into the coronary sinus under fluoroscopic examination. Another catheter was introduced into the right carotid artery and placed in the left ventricle.

Lead II of the surface electrocardiogram, heart rate, arterial and left ventricular pressure and its first derivative (dP/dt) were continuously recorded on a computer (MacIntosh Power PC) using a data acquisition system (MacLab 8 channels, ADInstruments).

A thoracotomy was performed at the 3rd intercostal space. The right stellate ganglion was isolated by ligating the sympathetic chain upstream and downstream, and the nerve branches to the heart were stimulated (10 V, 10 ms) during 60 s with bipolar platinum electrodes. The stimulation frequency (1–4 Hz) was adapted in order to reach a HR increase ranging between 50 and 80 beats min⁻¹ in control conditions.

An heparin injection (Choay, 5000 UI) was performed at the beginning of the experimental protocol.

Catecholamine measurement

Noradrenaline and adrenaline concentrations in the arterial and coronary sinus blood were determined by the HPLC technique after isolation by the alumina adsorption technique (Eriksson, 1993). The chromatographic system consisted of a pump (model 501, Chromatofield), a C₁₈ reverse phase column (Lichrospher, 250 × 4 mm, Merck) and an electrochemical detector (Coulochem 5100A, ESA). Dihydroxybenzylamine (Sigma) was used as the internal standard.

Experimental groups

Five dogs were treated successively with intravenous injection of R- α -methyl-histamine (Bioprojet, France) at doses of 0.2 and 2 μ mol kg⁻¹ h⁻¹ and finally with R- α -methyl-histamine 2 μ mol kg⁻¹ h⁻¹ following injection of SC 359 (Ciproxifan, cyclopropyl 4-(3-(1H-imidazol-4-yl)propoxy)phenyl)ketone, 1 mg kg⁻¹ base, i.v.) (Bioprojet, France), a specific H₃-antagonist (Figure 1).

Twelve dogs were treated successively with intravenous injection of BP 2.94 (Bioprojet, France) at doses of 0.1 and 1 mg kg⁻¹. Seven dogs were then treated with SC 359 (1 mg kg⁻¹ base, i.v.) (Bioprojet, France) and the remaining five dogs served as controls and were treated with saline instead of SC 359 (Figure 1).

Figure 1 Experimental protocol. Arrows represent times for haemodynamic measurements and blood collection before and 30 s after the beginning of right cardiac sympathetic stimulation. R-HA 0.2: R- α -methyl-histamine at 0.2 μ mol kg⁻¹ h⁻¹ and R-HA 2 at 2 μ mol kg⁻¹ h⁻¹, BP 0.1: BP 2.94 at 0.1 mg kg⁻¹ and BP 1 at 1 mg kg⁻¹, SC: SC 359 at 1 mg kg⁻¹.

Experimental protocol

Haemodynamic measurements and blood collection (5 ml) into the coronary sinus and aorta were realized before and 30 s after the beginning of each nerve stimulation. Cardiac nerve stimulation was performed in control conditions, 15 min after treatment with BP 2.94 or SC 359 and 10 min after the beginning of each R- α -methyl-histamine infusion (Figure 1).

Statistical analysis of data

In order to compare control and agonist-treated groups, one- or two-way analyses of variance followed by *post hoc* multiple comparison Tukey tests were performed when normality was respected. When it was not, non parametric Kruskal–Wallis tests with multiple comparison Dunn's tests were used. To compare antagonist-treated groups to corresponding agonist-treated groups, paired Student *t*-test were used (SigmaStat statistical software v.2.0, Jandel Scientifics). Statistical significance was set at $P \leq 0.05$.

Results

Haemodynamic parameters

In control conditions, right cardiac sympathetic nerve stimulation induced an increase in heart rate (185 ± 6 vs

Figure 2 Increase in heart rate (HR) and left ventricular dP/dt upon right cardiac sympathetic nerve stimulation (means $\pm$ s.e.mean) in control conditions (CTL), and left panels: 10 min after treatment with R- α -methyl-histamine at 0.2 μ mol kg⁻¹ h⁻¹ (R-HA 0.2) and at 2 μ mol kg⁻¹ h⁻¹ before (R-HA 2) and after SC 359 at 1 mg kg⁻¹ base (R-HA 2 + SC), right panels: 15 min after treatment with BP 2.94 at 0.1 mg kg⁻¹ (BP 0.1) and 1 mg kg⁻¹ alone (BP 1) and 15 min after SC 359 at 1 mg kg⁻¹ base (BP 1 + SC). * $P \leq 0.05$ vs CTL, # $P < 0.05$ vs R-HA 0.2 or BP 0.1, \$ $P < 0.05$ vs R-HA 2 or BP 1.

113 ± 12 beats min⁻¹ before stimulation, $P \leq 0.001$), left ventricular pressure (145 ± 10 vs 112 ± 7 mmHg, $P \leq 0.001$) and dP/dt (3800 ± 350 vs 2400 ± 200 mmHg s⁻¹, $P \geq 0.001$) (Figure 2).

Treatment with R- α -methyl-histamine dose-dependently reduced the heart rate increase and significantly reduced the increase in contractility. Those effects were antagonized by concomitant administration of SC 359 (Figure 2). Treatment with BP 2.94 at 0.1 and 1 mg kg⁻¹ also dose-dependently and significantly reduced the increases in heart rate, left ventricular pressure and contractility (Figure 2). Treatment with SC 359 inhibited the effects of the BP 2.94 restoring the response to sympathetic stimulation (Figure 2). The response to BP 2.94 (1 mg kg⁻¹) was maintained for at least 30 min, since a similar response was obtained at 15 and 30 min post-dosing in the saline treatment group (Table 1). Figure 3 shows typical tracings of the heart rate and dP/dt response to sympathetic stimulation in presence of the H₃-receptor agonists and antagonist.

Administration of R- α -methyl-histamine or BP 2.94 tended to decrease or significantly decreased basal heart rate and dP/dt (Figure 4), mean arterial pressure and left ventricular pressure (data not shown). On the opposite, SC 359 significantly increased these parameters (Figure 4).

Catecholamine concentrations

Right cardiac sympathetic nerve stimulation induced an increase in coronary sinus noradrenaline concentration (461 ± 73 vs 115 ± 32 pg ml⁻¹ before stimulation, $P \leq 0.001$). Coronary sinus adrenaline and arterial noradrenaline and adrenaline concentrations were not modified by the stimulation (data not shown).

Treatment with R- α -methyl-histamine at 0.2 and 2 mg kg⁻¹ significantly reduced cardiac noradrenaline release upon cardiac sympathetic nerve stimulation (Figure 5). BP 2.94 at 0.1 mg kg⁻¹ and 1 mg kg⁻¹ also significantly reduced it (Figure 5). The effects of both drugs were reversed by SC 359 (Figure 5). Saline administration *in lieu* of SC 359 did not affect the effect of BP 2.94 (Table 1).

Discussion

Our study provides the first demonstration of the existence of prejunctional H₃-receptors on cardiac sympathetic nerve endings in the dog. Their stimulation by R- α -methyl-histamine or BP 2.94 can inhibit the effects of sympathetic stimulation by reducing cardiac noradrenaline release and its associated haemodynamic effects.

Table 1 Reversal by SC 359 but not by saline of the effects of BP 2.94 on the haemodynamic response to right cardiac sympathetic nerve stimulation

Treatment	HR (beats min ⁻¹)	Increase in dP/dt (mmHg s ⁻¹)	NA (pg ml ⁻¹)
BP 1	31 ± 8	500 ± 200	12 ± 11
BP 1 + SC	56 ± 7*	1300 ± 300*	123 ± 60*
BP 1 + saline	40 ± 4	500 ± 100	0 ± 1

Data are means ± s.e.mean. HR: heart rate, dP/dt: first derivative of the left ventricular pressure, NA: coronary sinus noradrenaline concentration, BP 1: BP 2.94 at 1 mg kg⁻¹; BP 1 + SC: BP 2.94 at 1 mg kg⁻¹ followed by SC 359 at 1 mg kg⁻¹ base and BP 1 + saline: BP 2.94 at 1 mg kg⁻¹ followed by saline. * $P \leq 0.05$ vs BP 1.

The model of cardiac sympathetic nerve stimulation used in this study was first described by Yamaguchi *et al.* (1975), who showed that it can be a useful tool for the *in vivo* study of the role of the sympathetic nervous system in the regulation of cardiovascular function. It has also been used to demonstrate the prejunctional modulatory effects of various agents (Uchida *et al.*, 1984; Yamaguchi *et al.*, 1986). This model permits a selective cardiac sympathetic stimulation since increases in heart rate and in left ventricular pressure and contractility are seen without significant changes in mean arterial pressure. There is a correlation between this haemodynamic response and noradrenaline release into the coronary sinus (Yamaguchi *et al.*, 1975). Our results are in accordance with this observation.

Prejunctional H₃-receptors have been identified on sympathetic nerve endings in many species such as the mouse (Schlicker & Marr, 1997), rat (Godlewski *et al.*, 1996), guinea-pig (Endou *et al.*, 1994), cat (Schlicker *et al.*, 1994) and man (Imamura *et al.*, 1995). All these studies report a reduction in noradrenaline release and/or sympathetic response by H₃-receptor stimulation. The signalling pathway of H₃-receptor

Figure 3 Tracings representing the changes in heart rate and left ventricular dP/dt upon right cardiac sympathetic nerve stimulation in control conditions (CTL) and upper panel: 10 min after treatment with R- α -methyl-histamine at 0.2 (R-HA 0.2) and at 2 μ mol kg⁻¹ h⁻¹ before (R-HA 2) and after SC 359 at 1 mg kg⁻¹ base (R-HA 2 + SC), lower panel: 15 min after treatment with BP 2.94 at 0.1 mg kg⁻¹ (BP 0.1) and 1 mg kg⁻¹ alone (BP 1) and 15 min after SC 359 at 1 mg kg⁻¹ base (BP 1 + SC).

Figure 4 Heart rate (HR) and left ventricular dP/dt variation (means $\pm$ s.e.mean) induced by treatment with, left panels: R- α -methyl-histamine at 0.2 $\mu\text{mol kg}^{-1} \text{h}^{-1}$ (R-HA 0.2) and at 2 $\mu\text{mol kg}^{-1} \text{h}^{-1}$ before (R-HA 2) and after SC 359 at 1 mg kg^{-1} base (R-HA 2+SC), right panels: BP 2.94 at 0.1 mg kg^{-1} (BP 0.1) and 1 mg kg^{-1} alone (BP 1) and 15 min after SC 359 at 1 mg kg^{-1} base (BP 1+SC). * $P \leq 0.05$.

stimulation has not yet been elucidated but is known to depend on Gi/Go protein stimulation and N-type Ca²⁺ channel opening (Endou *et al.*, 1994) but not on AMPc synthesis (Schlicker *et al.*, 1994). Endou *et al.* (1994) on isolated guinea-pig atria and Imamura *et al.* (1994) on isolated guinea-pig hearts, have demonstrated that H₃-receptor stimulation by R- α -methyl-histamine reduces the inotropic and chronotropic response to sympathetic stimulation by inhibiting noradrenaline release. Our results are in accordance with these studies since R- α -methyl-histamine and BP 2.94 induced a dose-dependent decrease in electrically-evoked noradrenaline release and haemodynamic response. This effect was due to H₃-receptor stimulation since R- α -methyl-histamine (a selective H₃-receptor agonist) induced a clear inhibitory effect that was antagonized by SC 359. Indeed, SC 359 is a very potent (CI₅₀ for histamine release: 9 ± 2 vs 75 ± 19 nM for thioperamide) and selective (pK = 9.3 vs 5 for other histaminergic, adrenergic or serotonergic receptors) competitive H₃-receptor antagonist (Ligneau *et al.*, 1998). Our results confirm that BP 2.94 is a potent H₃-receptor agonist with a longer half-life than R- α -methyl-histamine since a single bolus was able to stimulate H₃-receptors for at least 30 min. Indeed, the recovery observed following SC 359 administration cannot be explained by a decreased activity of BP 2.94 since it was not observed when saline was injected *in lieu* of SC 359. In fact, BP 2.94 remained effective in inhibiting noradrenaline release 1 h after its administration.

Figure 5 Increase in cardiac noradrenaline release (veno-arterial difference) upon right cardiac sympathetic nerve stimulation (means $\pm$ s.e.mean) in control conditions (CTL) and left panel: 10 min after treatment with R- α -methyl-histamine at 0.2 $\mu\text{mol kg}^{-1} \text{h}^{-1}$ (R-HA 0.2) and at 2 $\mu\text{mol kg}^{-1} \text{h}^{-1}$ before (R-HA 2) and after SC 359 at 1 mg kg^{-1} base (R-HA 2+SC), right panel: 15 min after treatment with BP 2.94 at 0.1 mg kg^{-1} (BP 0.1) and 1 mg kg^{-1} alone (BP 1) or 15 min after SC 359 at 1 mg kg^{-1} base (BP 1+SC). * $P \leq 0.05$ vs CTL, \$ $P \leq 0.05$ vs BP 1.

Basal cardiovascular effects of H₃ agonists vary according to the species. In the guinea-pig and in the rabbit, R- α -methyl-histamine induces bradycardia and hypotension (McLeod *et al.*, 1994) while in the rat, H₃ agonists have no effects (Corrucci *et al.*, 1995) at least not at the doses where they are selective for H₃-receptors. Our results show that, in the dog, H₃-receptor activation by BP 2.94 decreased heart rate and tended to reduce contractility and arterial pressure. H₃-antagonists fail to induce cardiovascular effects in the guinea-pig, rabbit and rat (Corrucci *et al.*, 1995). We observed that, in the dog, SC 359 induced an important vasopressive response and a tachycardia after R- α -methyl-histamine or BP 2.94. This can probably be explained by an antagonism of the effects of the H₃-agonists but also of the action of endogenous histamine on H₃-receptors. This suggests that in the dog, H₃-receptors are constitutionally functional and activated by endogenous histamine, thus exerting a basal retrocontrol on noradrenaline release. However, H₃-receptors remain responsive to exogenous agonists that can exert a more pronounced effect.

The important sympathoinhibitory action and good bioavailability of BP 2.94 suggests a potential clinical use in conditions associated with enhanced sympathetic tone such as myocardial ischaemia or heart failure. Indeed, H₃-agonists have been shown to reduce ischaemia-induced noradrenaline release in the isolated guinea-pig heart (Imamura *et al.*, 1996) and in isolated human atria (Hatta *et al.*, 1997). Also, H₃-receptor desensitization could contribute to the elevated plasma noradrenaline levels in cardiac failure (Seyedi *et al.*, 1997).

In conclusion, the present study shows that functional H₃-receptors inhibiting noradrenaline release are present on cardiac sympathetic nerve endings in the dog and can be activated by H₃-receptor agonists R- α -methyl-histamine and its prodrug BP 2.94.

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