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Positive inotropic effects of histamine in anaesthetized dogs

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1 The cardiovascular effects of histamine were examined in dogs anaesthetized with pentobarbitone

2 The effect of histamine on heart rate, blood pressure, left ventricular pressure, dP/dt_{max} and dP/dt: IIT (integrated isometric tension) was compared in the presence and absence of autonomic reflexes and blood pressure control.

3 In innervated animals with no attempt to control blood pressure, histamine produced dose-dependent decreases in blood pressure and heart rate and either positive or negative inotropic actions.

4 When autonomic reflexes were abolished, this variability in inotropic response was reduced and histamine produced a slight positive inotropic response. There was a decrease in blood pressure and a positive chronotropic response to histamine.

5 When blood pressure was controlled and the cardiac nerves were intact, histamine produced a decrease in heart rate. However, in the denervated animals, there was a slight increase in heart rate.

6 Inotropic responses to histamine in the blood pressure controlled groups were less variable than when blood pressure was uncontrolled. In all of these animals there was an increase in contractility, the increase being more marked in the denervated group.

7 The H_2-receptor agonist impromidine produced a positive inotropic action in intact animals with uncontrolled blood pressure.

Introduction

The results from early studies in isolated tissues and heart-lung preparations suggested that histamine exerts a positive inotropic effect in canine myocardium (for references see Levi *et al.*, 1982). Although the effects of histamine on isolated hearts have been widely studied, there are few descriptions of the cardiac actions of histamine under *in vivo* conditions. This may be due to the fact that under these circumstances inotropic responses to histamine are difficult to evaluate, since the systemic vascular action of histamine and consequent changes in blood pressure may influence cardiac contractility either directly or indirectly.

Reinhardt *et al.* (1980) examined the effect of histamine in the intact dog. Histamine produced a dose-dependent decrease in cardiac contractility which was accompanied by a fall in mean aortic pressure. When arterial pressure was held constant by a stabilizer system, histamine evoked slight positive inotropic effects which were antagonized by cimetidine. The authors concluded that the ventricular myocardium of the dog contains H_2-receptors mediating positive inotropic responses, which may be masked in the presence of an intact autonomic cardiovascular system.

Although histamine produces a positive chronotropic effect in most species, the effects of histamine on heart rate in the dog have not been extensively investigated. It has been suggested that the positive chronotropic effect of histamine in the dog is only observed when it is injected in high doses in the vicinity of the sinus node (Levi *et al.*, 1982). Others (Lokhandwala, 1978b) claim that the increase in heart rate observed may be a reflex response to the fall in arterial blood pressure during histamine administration. Furthermore, histamine has been shown to reduce noradrenaline output from sympathetic nerves in dogs (Lokhandwala, 1978b) and this presynaptic effect may confound measurements of the direct chronotropic activity of histamine *in vivo*. In order to evaluate the direct effects of histamine on the canine myocardium it is necessary to reduce or remove these indirect effects.

This paper describes the results from experiments in which the cardiovascular effects of histamine were examined in anaesthetized dogs with no attempt to control the indirect effects and compares those data

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with the results from a group of animals in which the blood pressure was controlled and the heart was surgically denervated. In addition, impromidine, a specific H_2-receptor agonist, was administered to a group of animals in which no attempt was made to control blood pressure.

Methods

Mongrel dogs of either sex (15–25 kg) were anaesthetized with sodium pentobarbitone (30 mg kg^{-1}, i.v.). Supplementary doses of anaesthetic (1–2 mg kg^{-1}) were administered as required. The animals were incubated and artificially ventilated with room air (Palmer ventilator). The left femoral vein was cannulated for the administration of drugs and a cannula was inserted into the left femoral artery to measure arterial blood pressure (Statham P23AC transducer). The cannula was kept patent with heparinised saline (500 units ml^{-1}) and zero pressure was set at mid-chest level.

Heart rate was measured by a tachograph (Grass 7PdD) triggered by the R-wave of the Lead II ECG and continuously recorded on the polygraph. A thoracotomy was performed through the fifth intercostal space. Left ventricular pressure (LVP) was measured by a miniature transducer (Konigsberg P13) implanted in the left ventricle through a stab incision and secured with a purse-string suture. The first derivative of LVP, *dP/dt*, was obtained using an active differentiating circuit. Only the *dP/dt* derived from the rising LVP was recorded and continuously displayed on the oscilloscope.

The index of contractility used in this study was obtained by the division of maximum *dP/dt* by the time integral of isovolumic ventricular pressure during the period from the R-wave of the ECG to the peak *dP/dt* (Goodman *et al.*, 1972). The index was computed, beat-by-beat, by an on-line digital computer (PDP 11/34, Digital Equipment Australia).

After completion of the surgical instrumentation, the dogs were allowed to stabilize for 30–40 min before the infusion of histamine. Blood pressure, heart rate, ECG, LVP, *dP/dt* and contractility (*dP/dt*: IIT) were recorded on a polygraph (Grass Model 7C).

In group A ($n = 14$) the effects of histamine on the cardiovascular system, with autonomic innervation intact, were evaluated. In group B ($n = 6$) a midsternal incision was performed to allow access to both the left and right stellate ganglia. The ganglia were isolated and removed. The vagi were sectioned in the neck. Cardiac denervation was confirmed by the absence of the baroreceptor reflex response to 30 s bilateral carotid occlusion. The animals were heparinized (5,000 units) and both carotid arteries were cannulated and connected to a blood reservoir (2 litres). The height of the reservoir could be adjusted and was used to control blood pressure at the desired level. In these experiments a donor dog was heparinized (5,000 units) and bled before the start of the experimental procedure. The blood was added to the reservoir so that when vasodilatation occurred, blood from the reservoir bottle flowed into the animal and the desired pressure was maintained.

In group C ($n = 6$) blood pressure was controlled (as for group B) without accompanying denervation. In group D ($n = 6$) cardiac denervation was performed without attempting to control blood pressure.

In groups A-D, histamine acid phosphate (Sigma) was infused i.v. (McGaw Volumetric Infusion Pump) in increasing doses. Infusion at each dose level was maintained for 5 min. This period of infusion for each dose was selected in order to complete the dose-response curve within the time in which it could be assumed there would be no deterioration of the animal. In another group of animals (group E, $n = 8$) the cardiovascular effects of bolus doses of impromidine (0.2–5.0 nmol kg^{-1}) were evaluated.

Data from each group were expressed as mean values (± s.e.mean). Students *t* test (two-tailed for non-correlated data) was used to compare the resting values in the different groups. The significance level for the *t* tests was taken as 0.01 to avoid obtaining false positive results due to multiple testing. In this way, the experiment-wise type I error will be kept at approximately 0.05. Repeated analyses of variance were used as the test of statistical significance of the effects of pressure regulation and denervation. Results were considered significant when $P < 0.05$. Post-hoc tests were performed where there was a significant change in responses. The significance level for these tests was taken as 0.01, for reasons outlined above.

Results

The cardiovascular actions of histamine were examined in the presence (Groups A and C) and absence (Groups B and D) of autonomic reflexes. In groups B and C blood pressure was maintained at a constant level by use of a blood reservoir. The resting values for contractility, heart rate and mean blood pressure for dogs in each group were pooled, the mean (± s.e.mean) values were calculated and are shown in Table 1. Except for a lower resting blood pressure in group C and heart rate in group D, the resting cardiovascular parameters were not significantly ($P > 0.01$) influenced by denervation or blood pressure control.

Blood pressure uncontrolled

Histamine caused a dose-dependent ($P < 0.05$)

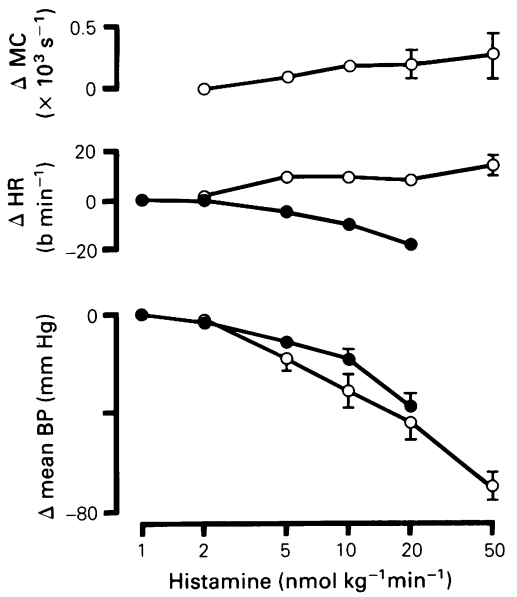

Figure 1 Mean responses to histamine in dogs with innervated (●) and denervated (○) hearts. Blood pressure (BP) was uncontrolled. HR = heart rate (beats-min^{-1}); MC = myocardial cautractility.

decrease in mean blood pressure in both innervated and denervated animals (Figure 1). This decrease was not significantly ($P > 0.05$) altered by denervation. It can be seen (Figure 1) that in the denervated group a higher dose of histamine was infused. The response to the highest dose could not be included in the statistical analysis, but shows that the dose-response relationship was continued.

The chronotropic responses to histamine are also shown in Figure 1. Histamine produced a dose-dependent decrease in heart rate in the innervated animals and an increase in heart rate in the denervated animals. This difference in responses in the two groups was statistically significant at 20 nmol kg^{-1} min^{-1}.

There was marked variability in the inotropic responses of the animals in the innervated group (Group A) and the responses for each individual animal are presented in Figure 2. Denervation greatly reduced this variability and the inotropic responses for this group were pooled and the mean (± s.e.mean) response at each dose level are presented in Figure 1. In these animals, although the dose-dependence was not statistially significant, histamine produced an increase in contractility.

Blood pressure controlled

When blood pressure was controlled, the cardiovascular responses to histamine administration differed from those observed in animals with uncontrolled blood pressure. Control of blood pressure permitted higher doses of histamine (2–100 nmol kg^{-1} min^{-1}) to be infused. At the highest dose of histamine all of the blood in the reservoir (2 litres) had drained into the experimental animals.

Although blood pressure was 'controlled' by the blood reservoir, histamine produced a slight fall in mean blood pressure, which was similar in the innervated and denervated animals (Figure 3). At the high dose of 20 nmol kg^{-1} min^{-1}, the fall in mean blood pressure in these 'controlled' animals was < 10 mmHg, whereas in the uncontrolled animals blood pressure fell by 35–50 mmHg.

Figure 3 shows the chronotropic responses to histamine infusion in the innervated and denervated animals with controlled blood pressure. In the innervated dogs, histamine produced a decrease in heart rate, which just reached statistical significance. In the denervated animals there was a slight increase in heart rate in response to histamine. The difference in the responses increased with increasing doses of histamine and was statistically significant at doses in > 5 nmol kg^{-1} min^{-1} (except at 50 nmol kg^{-1} min^{-1}, due to the large standard error for the innervated group).

The inotropic responses to histamine in the blood pressure controlled groups are shown in Figure 3. Both groups had an increase in myocardial contractility, increase was marked in the denervated group and this difference was significant. In the innervated

Table 1 Resting cardiovascular parameters before infusion of histamine in anaesthetized dogs

Group	n	*Mean blood pressure* (mmHg)	*Heart rate* (beats min^{-1})	*Contractility* (× 10^3 s^{-2})
A	14	113 ± 4	150 ± 5	1.50 ± 0.1
B	6	105 ± 9	142 ± 13	1.40 ± 0.2
C	6	95 ± 3	146 ± 12	1.30 ± 0.1
D	6	115 ± 8	124 ± 6	1.40 ± 0.1
E	8	115 ± 7	131 ± 10	1.40 ± 0.2

n = number of dogs in each group. Values are mean ± s.e.mean.

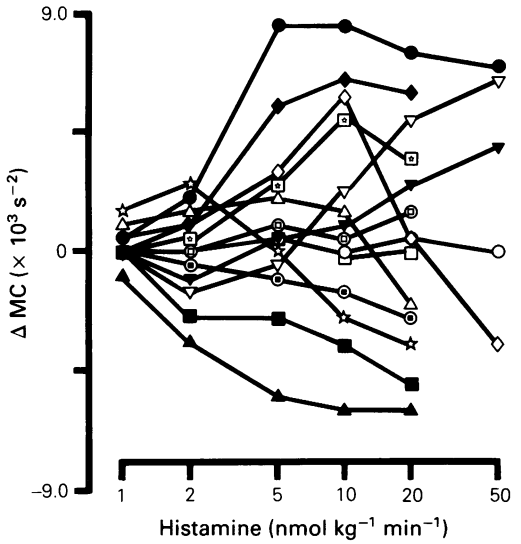

Figure 2 Inotropic responses to histamine in anaesthetized dogs; (each dog is represented by a different symbol). MC = myocardial cautractility.

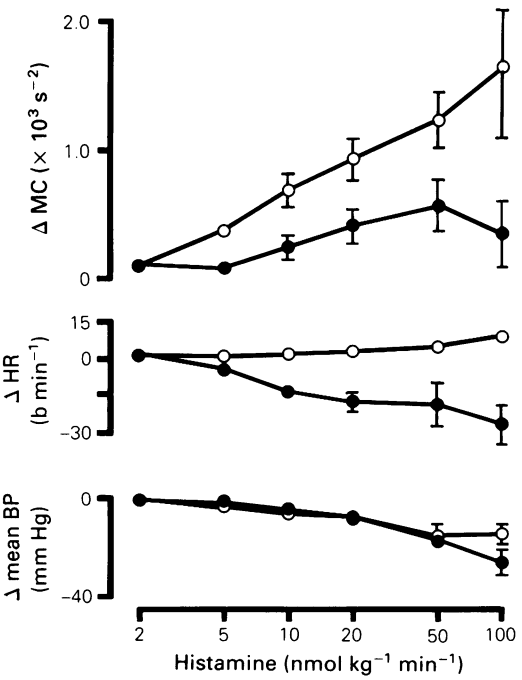

Figure 3 Mean responses to histamine in dogs with innervated (●) and denervated (○) hearts (BP controlled). Abbreviations as in Figure 1.

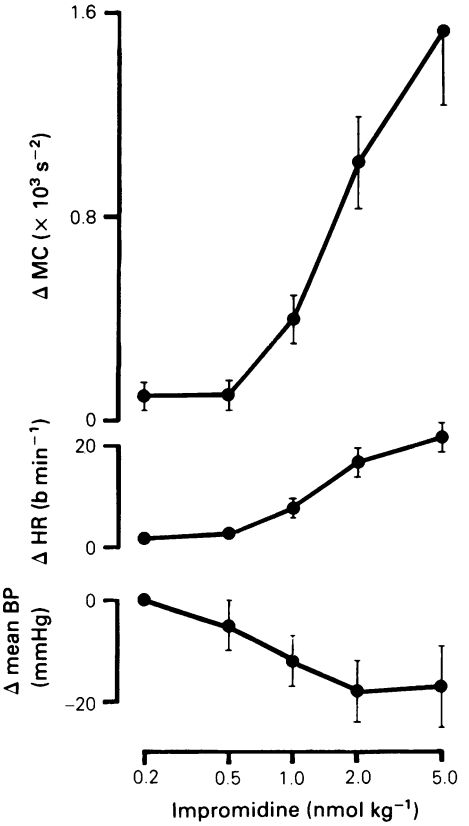

Figure 4 Mean responses to impromidine in anaesthetized dogs. Abbreviations as in Figure 1.

group, the maximum inotropic response occurred at 50 nmol kg^{-1} min^{-1}, whereas in the denervated animals, contractility continued to increase up to the maximum dose of 100 nmol kg^{-1} min^{-1}.

Blood pressure control markedly increased the inotropic response in the denervated animals. There was approximately 0.30 × 10^3 s^{-2} increase in contractility at 50 nmol kg^{-1} min^{-1} in the uncontrolled group (Group D) whereas this was increased 4 fold when blood pressure was controlled (Group B).

Impromidine series

Impromidine caused a dose-dependent decrease in mean blood pressure and increase in heart rate and contractility (Figure 4). The inotropic action of impromidine in these intact animals in which there was no attempt to control blood pressure was different from that of histamine under similar conditions. In fact the inotropic response to impromidine closely resembled the histamine response in denervated animals with blood pressure controlled.

Discussion

When no attempt was made to control blood pressure, histamine produced a marked vasodepressor response, similar to that observed in several other studies (Hirschowitz *et al.*, 1979; Harvey & Owen, 1984). When autonomic reflexes were removed, the vasodepressor effect was unchanged, confirming that this action of histamine is direct (Harvey & Owen, 1984). Harvey & Owen (1984), using an antagonist of both H_1- and H_2-receptors found that the depressor response to histamine was mediated by both types of receptor. These authors suggested that the response is time-dependent and that within 1 min of starting the infusion, the vasodilator response was predominantly via H_1-receptors. When the infusions exceed 2 or 3 min, the sustained response was via the H_2-receptors.

Contrary to previous studies in dogs anaesthetized with pentobarbitone, in which an increase in heart rate (possibly as a reflex response to the fall in blood pressure) was found (Lokhandwala, 1978b; Nandiwada *et al.*, 1980), histamine produced a decrease in heart rate in the present experiments. The negative chronotropic response may have been the result of histamine-induced inhibition of sympathetic nerve function reported by Lokhandwala (1978a) and Kimura & Satoh (1983). This possibility is supported by the observation that a positive chronotropic response to histamine was observed in denervated animals.

Hirschowitz *et al.* (1980) found that histamine caused an increase in heart rate in conscious dogs. Since heart rate had already begun to increase before systolic blood pressure had fallen, these authors concluded that the positive chronotropic response was a direct, dose-dependent effect of histamine on the pacemaker. The present findings in denervated dogs support the claim for a direct positive chronotropic action of histamine.

In some of the innervated animals, histamine produced a positive inotropic effect, while in others there was a reduced contractility, results similar to those observed by Levi *et al.* (1982). When autonomic reflexes were abolished, this variability in inotropic response was reduced and histamine consistently produced a slight positive inotropic response. Since this response occurred in the absence of cardiac nerves, it was likely to be a direct action of histamine.

Although it was not possible to avoid changes in blood pressure completely, the depressor responses in animals with controlled blood pressure were very much less than those in Groups A and D. When arterial pressure was held constant, histamine induced a reproducible, positive inotropic response. Similar results were obtained by Reinhardt *et al.* (1980) when they controlled blood pressure by a stabilizer system. Since blood pressure was controlled, the inotropic responses observed in this group could not be due to alterations in afterload. In addition, since there was no rise in left ventricular end-diastolic pressure, the increased contractility could not have been due to increases in preload. It would appear that the positive inotropic action of histamine is masked in the presence of autonomic reflexes, since cardiac denervation (Group B) potentiated this response to histamine.

Histamine produced similar decreases in heart rate in intact animals regardless of blood pressure control. Therefore the negative chronotropic effect was independent of changes in blood presure. The observation that after denervation there was a positive chronotropic effect suggests that, although the direct effect of histamine is to increase heart rate, this action is modified in the presence of autonomic nerves.

The more marked increase in contractility in the pressure controlled animals may have been due in part, to the extra volume of blood which entered the circulation from the reservoir bottle. However, even in the absence of pressure control, a significant increase in contractility was seen in denervated animals, which suggests that at least part of this response was directly due to histamine on the heart. Furthermore, results from the experiments with impromidine indicate that in intact animals with uncontrolled blood pressure, H_2-receptor stimulation results in marked inotropic responses.

In conclusion, the results from these experiments have shown that if blood pressure is held constant and cardiac denervation performed, a positive inotropic action of histamine can be demonstrated in the dog. It is probable that this response is mediated via H_2-receptors. Further experiments are necessary to evaluate the contribution of the baroreceptor reflexes and of possible presynaptic effects.

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