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THE EFFECTS OF HISTAMINE AND SOME HISTAMINE-LIKE AGONISTS ON BLOOD PRESSURE IN THE CAT

D.A.A. OWEN

Department of Pharmacology, The Research Institute, Smith Kline & French Laboratories Limited Welwyn Garden City, Hertfordshire

1 The effects of histamine on blood pressure have been compared with the effects caused by four histamine-like agonists in anaesthetized cats.

2 It has been confirmed that the depressor responses to histamine involve both H_1- and H_2-receptors: depressor responses also follow the administration of selective H_1- and H_2-receptor agonists.

3 2-Methylhistamine, in doses up to 1×10^{-7} mol/kg, lowers blood pressure by interaction with H_1-receptors. Larger doses of 2-methylhistamine also lower blood pressure but this may involve H_2-receptors.

4 4-Methylhistamine, in doses up to 1×10^{-7} mol/kg, lowers blood pressure by interaction with H_2-receptors. Larger doses of 4-methylhistamine also lower blood pressure but this may involve H_1-receptors.

5 2-(2-Aminoethyl)pyridine and 2-(2-aminoethyl)thiazole both lower blood pressure by interaction with H_1-receptors only.

6 The potential value and limitations of these compounds as tools to investigate the cardiovascular effects of histamine are discussed.

Introduction

Many compounds have been described with histamine-like activity (for example Jones, 1966). Some of these histamine-like agonists interact selectively with either H_1- or H_2-receptors. Three agonists, 2-methylhistamine (Black, Duncan, Durant, Ganellin & Parsons, 1972; Durant, Ganellin & Parsons, 1975), 2-(2-aminoethyl)-pyridine and 2-(2-aminoethyl)thiazole (Lee & Jones, 1949; Grossman, Robertson & Rosiere, 1952; Durant *et al.*, in press), have been shown to interact selectively with H_1-receptors whereas 4-methylhistamine selectively interacts with H_2-receptors (Black *et al.*, 1972; Durant *et al.*, 1975).

This paper describes the effects of histamine and these selective histamine-like agonists on blood pressure in the cat. Histamine lowers blood pressure in the cat—a response which involves both H_1- and H_2-receptors (Black *et al.*, 1972; Owen & Parsons, 1974).

Methods

Experiments have been made in cats, of either sex, body weight 1.3-2.5 kg, anaesthetized by an intraperitoneal injection of sodium pentobarbitone (60 mg/kg). The trachea was cannulated. Blood pressure was measured from the right femoral artery, with a Statham P23A blood pressure transducer, and monitored on a Devices Electronic writer. Drugs were administered via cannulae in the right femoral vein or right brachial vein. Dose-response curves were constructed for histamine and histamine-like agonists by intravenous injections of increasing doses at intervals of 5 minutes.

Two series of experiments were done. The purpose of the first series was to determine the selectivity of each of the agonists for cardiovascular histamine receptors. In each experiment, one or two of the agonists were compared with histamine. Dose-response curves to histamine and the agonists were obtained in

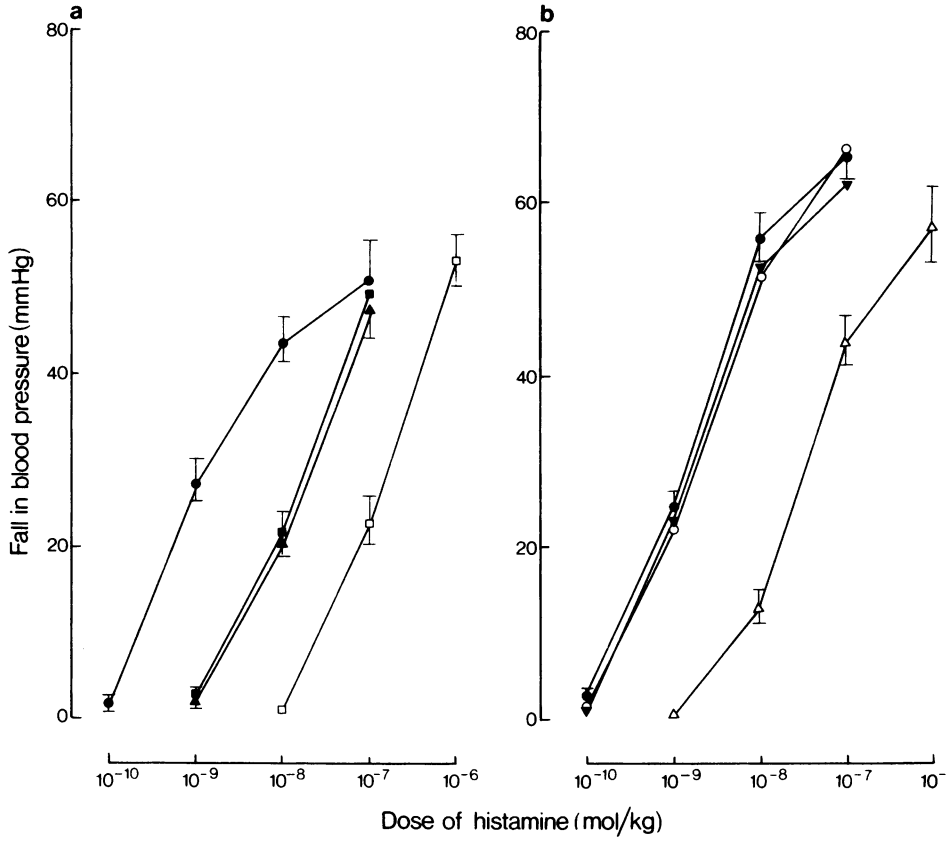

Figure 1 Anaesthetized cat blood pressure. The effect of mepyramine and metiamide on the depressor responses to histamine. (a) Effect of mepyramine alone and in combination with metiamide on the responses to histamine, $n = 11$. (●) Dose-response curve to histamine in the untreated cats; (■) after mepyramine 2.5×10^{-6} mol/kg; (▲) after mepyramine 2.5×10^{-5} mol/kg; (□) after treatment with mepyramine 2.5×10^{-5} mol/kg and metiamide 4×10^{-7} mol kg^{-1} min^{-1}. (b) Effect of metiamide alone and in combination with mepyramine on the histamine responses, $n = 11$. (●) Control dose-response curve; (○) after treatment with metiamide 4×10^{-7} mol kg^{-1} min^{-1}; (▼) after metiamide 2×10^{-6} mol kg^{-1} min^{-1}; (△) after metiamide 2×10^{-6} mol kg^{-1} min^{-1} and mepyramine 2.5×10^{-6} mol/kg. Vertical bars indicate s.e. mean.

untreated animals and then repeated after either H_1-receptor blockade with mepyramine or H_2-receptor blockade with metiamide. Mepyramine was given at two dose levels, 2.5×10^{-6} and 2.5×10^{-5} mol/kg. Displacement of the dose-response curves by mepyramine was evidence that the depressor responses were due to interaction with H_1-receptors. Metiamide was given by intravenous infusion at 4×10^{-7} mol kg^{-1} min^{-1} initially and then 2×10^{-6} mol kg^{-1} min^{-1}. Displacement of the dose-response curves by metiamide indicated interaction with H_2-receptors.

In the second series of experiments, made after determining the selectivity of the agonists for histamine receptors, the agonists were assayed for their depressor activity, relative to histamine under two conditions, firstly on H_1-receptors only during infusion of metiamide, 1×10^{-5} mol kg^{-1} min^{-1}, to block H_2-receptors and secondly on H_2-receptors only after injection of mepyramine, 2.5×10^{-5} mol/kg, to block H_1-receptors. Doses of histamine and the agonists were administered in random order. The results were treated by analysis of variance to provide estimates of potency.

Drugs used

Histamine acid phosphate (B.D.H.), mepyramine maleate (May & Baker), metiamide, 2-methylhistamine dihydrochloride, 4-methylhistamine

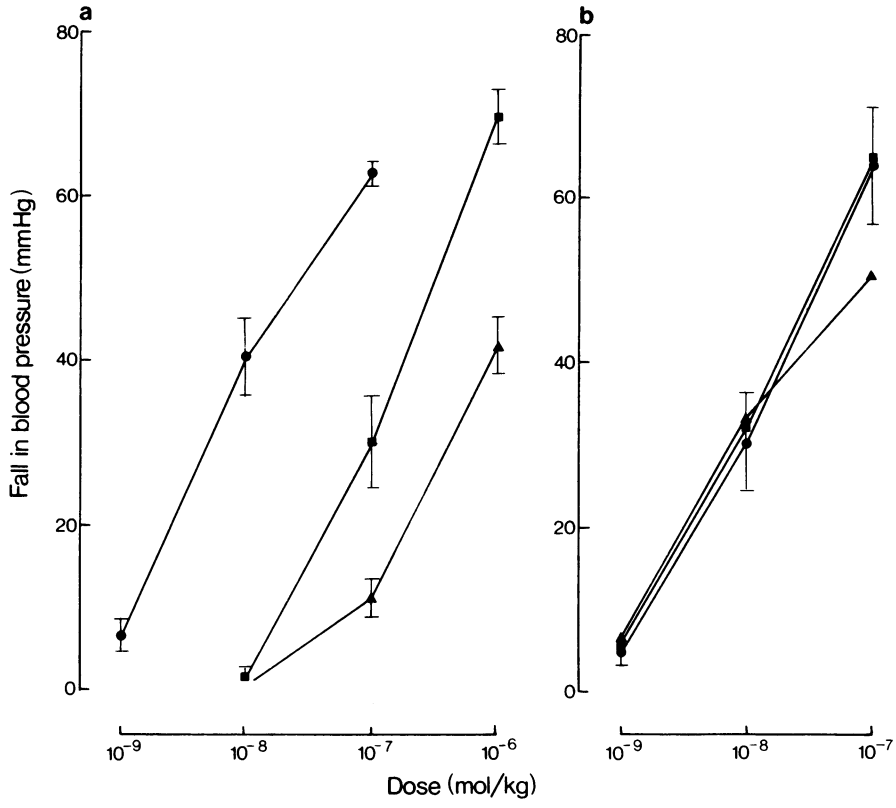

Figure 2 Anaesthetized cat blood pressure. The effect of two doses of mepyramine on the depressor responses to 2-methylhistamine (a), $n = 4$, and 4-methylhistamine (b), $n = 4$. (●) Dose-response curves before mepyramine; (■), after mepyramine, 2.5×10^{-6} mol/kg; (▲) after mepyramine, 2.5×10^{-5} mol/kg. Mepyramine causes dose-dependent displacement of the 2-methylhistamine dose-response curve but had no effect on the responses to 4-methylhistamine. Vertical bars indicate s.e. mean.

dihydrochloride, 2-(2-aminoethyl)pyridine dihydrochloride and 2-(2-aminoethyl)thiazole dihydrochloride all synthesized by S.K. & F. Laboratories Limited, Welwyn Garden City.

Solutions of metiamide were prepared by dissolving the base in 0.1 N HCl. The pH of the solution was then raised to 7 with 0.1 N NaOH and the solution made up to volume with 0.9% NaCl solution. All other drugs were dissolved in 0.9% NaCl solution.

Results

Selectivity of the agonists for histamine-receptors

Histamine Both H_1- and H_2-receptors are involved in the depressor responses to histamine in the cat (Black *et al.*, 1972; Owen & Parsons, 1974). This has been confirmed in the present series of experiments. Histamine caused dose-dependent depressor responses over the dose-range 1×10^{-10} to 1×10^{-7} mol/kg. The histamine dose-response curve could be displaced to the right by mepyramine (2.5×10^{-6} mol/kg) but not by metiamide alone (up to 2×10^{-6} mol kg^{-1} min^{-1}). The displacement caused by mepyramine achieved a maximum at which point further displacement of the dose-response curve could only be achieved by infusions of metiamide (4×10^{-7} mol kg^{-1} min^{-1} and 2×10^{-6} mol kg^{-1}; Figure 1).

2-Methylhistamine 2-Methylhistamine caused dose-dependent depressor responses over the dose-range 1×10^{-9} to 1×10^{-7} mol/kg. Administration of mepyramine (2.5×10^{-6} mol/kg) caused a displacement of the dose-response curve to the right. This displacement was comparable to the displacement of histamine dose-response

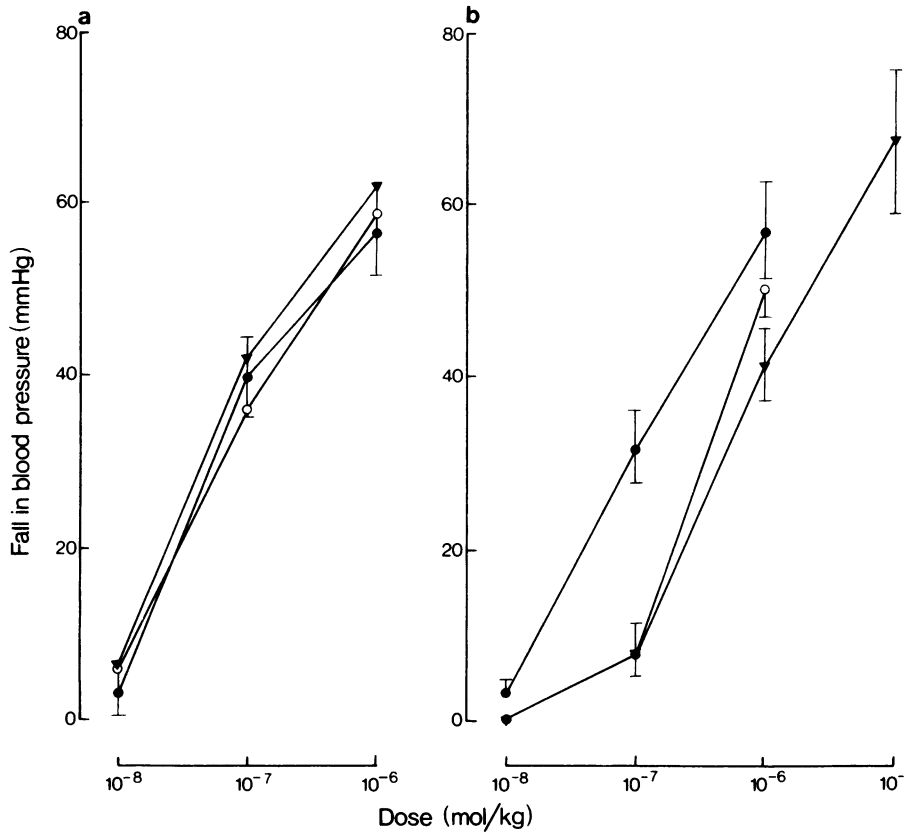

Figure 3 Anaesthetized cat blood pressure. The effect of two doses of metiamide on the depressor responses to 2-methylhistamine (a), $n = 4$, and 4-methylhistamine (b), $n = 4$. (•) Dose-response curves before metiamide; (○) during infusion of metiamide 4×10^{-7} mol kg^{-1} min^{-1}; (▼) during infusion of metiamide, 2×10^{-6} mol kg^{-1} min^{-1}. Vertical bars indicate s.e. mean.

curves by mepyramine (2.5×10^{-6} mol/kg). However, 2-methylhistamine differed from histamine because this dose of mepyramine did not cause maximal displacement of the dose-response curve. Increasing the dose of mepyramine to 2.5×10^{-5} mol/kg caused further displacement, to the right, of the 2-methylhistamine dose-response curve (see Figure 2). It was not possible to give a larger dose of mepyramine because of its toxic effects. It is likely that doses of 2-methylhistamine, greater than 1×10^{-7} mol/kg, administered in the presence of mepyramine (2.5×10^{-5} mol/kg), can interact with H_2-receptors, since administration of metiamide (4×10^{-7} mol kg^{-1} min^{-1}) caused a ' further displacement of the 2-methylhistamine dose-response curve.

Metiamide infusions (4×10^{-7} and 2×10^{-6} mol kg^{-1} min^{-1}) in the absence of mepyramine had no effect on the 2-methylhistamine dose-response curve (Figure 3).

These results indicate that the depressor responses to 2-methylhistamine are due to interaction with H_1-receptors. When large doses of 2-methylhistamine are given, in the presence of mepyramine, interaction with H_2-receptors can also occur.

4-Methylhistamine 4-Methylhistamine caused dose-dependent falls in blood pressure over the dose-range 1×10^{-8} to 1×10^{-6} mol/kg. The dose-response curve to 4-methylhistamine was not displaced by mepyramine (2.5×10^{-6} or 2.5×10^{-5} mol/kg; Figure 2). In contrast, metiamide (4×10^{-7} mol kg^{-1} min^{-1}) displaced the dose-response curve to the right. Increasing the dose of metiamide to 2×10^{-6} mol kg^{-1} min^{-1} caused no further displacement of the

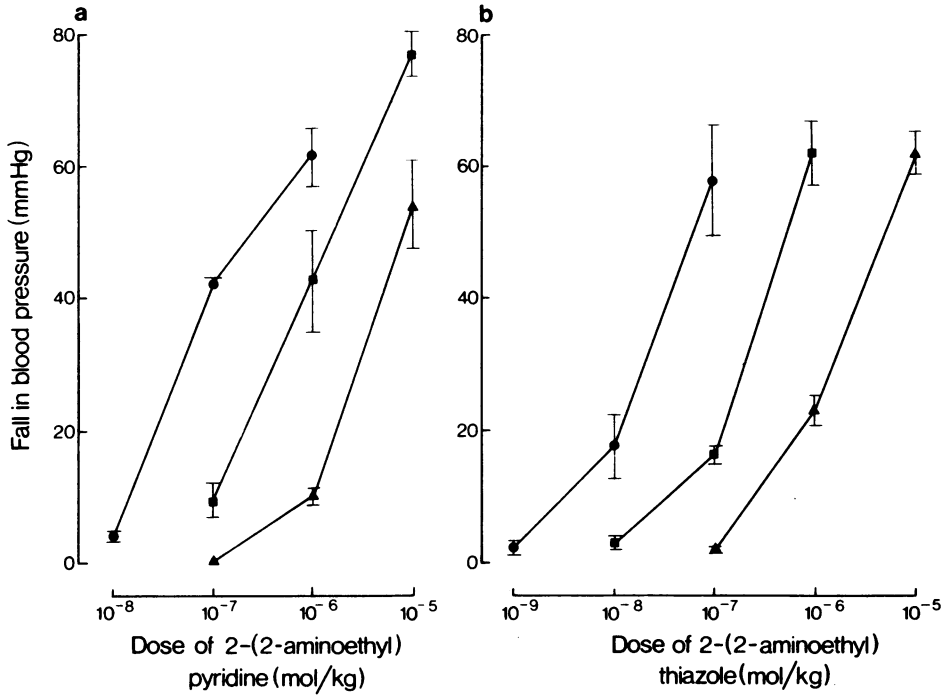

Figure 4 Anaesthetized cat blood pressure. The effect of two doses of mepyramine on the depressor responses to 2-(2-aminoethyl)pyridine (a), $n = 4$ and 2-(2-aminoethyl)thiazole (b), $n = 4$. (●) Dose-response curves before mepyramine; (■) after mepyramine 2.5×10^{-6} mol/kg; (▲) after mepyramine, 2.5×10^{-5} mol/kg. Vertical bars indicate s.e. mean.

dose-response curve (Figure 3). However, administration of mepyramine (2.5×10^{-6} mol/kg) during the continuing infusion of metiamide caused further displacement of the dose-response curve. These results indicate that 4-methylhistamine in doses up to 1×10^{-7} mol/kg causes depressor responses by interaction with H_2-receptors; larger doses of 4-methylhistamine can interact with H_1-receptors.

2-(2-Aminoethyl)pyridine 2-(2-Aminoethyl) pyridine caused dose-dependent depressor responses over the dose-range 1×10^{-8} to 1×10^{-6} mol/kg. Mepyramine (2.5×10^{-6} mol/kg and 2.5×10^{-5} mol/kg) caused dose-dependent displacements of the dose-response curve to the right (Figure 4). Metiamide (up to 2×10^{-6} mol kg^{-1} min^{-1}) had no effect on the depressor responses to 2-(2-aminoethyl)pyridine either in control cats or when larger doses of 2-(2-aminoethyl)pyridine were given in the presence of mepyramine. These results indicate that the depressor responses to 2-(2-aminoethyl)-pyridine are due entirely to interaction with H_1-receptors.

2-(2-Aminoethyl)thiazole 2-(2-Aminoethyl)thiazole caused dose-dependent falls in blood pressure over the dose-range 1×10^{-9} to 1×10^{-7} mol/kg. The dose-response curve was displaced to the right by mepyramine (2.5×10^{-6} mol/kg) and further to the right by increasing the dose of mepyramine 10-fold (Figure 4). Metiamide (up to 2×10^{-6} mol kg^{-1} min^{-1}) had no effect on dose-response curves obtained in untreated animals or in animals treated with mepyramine (2.5×10^{-5} mol/kg). These results indicate that the depressor responses to 2-(2-aminoethyl)thiazole are also due entirely to interaction with H_1-receptors.

Potency of the histamine-like agonists, relative to histamine

The potency of the agonists relative to histamine was measured on both H_1- and H_2-receptors (Table 1).

Table 1 Relative potency of histamine and some histamine-like agonists on cardiovascular H_1- and H_2-receptors

Agonist	*Relative Activity (95% confidence limits)*	
	H_1-receptors	*H_2-receptors*
Histamine	100	100
2-methylhistamine	18.2 (13.7-24.0)	3.0 (1.6-5.4)
4-methylhistamine	0.13 (0.07-0.25)	23.7 (12.9-43.6)
2-(2-aminoethyl)pyridine	0.9 (0.7-1.2)	Inactive
2-(2-aminoethyl)thiazole	7.9 (6.0-10.5)	Inactive

Discussion

Histamine causes dose-dependent depressor responses which involve both H_1- and H_2-receptors (Black *et al.*, 1972; Owen & Parsons, 1974; Black, Owen & Parsons, 1975). This has been confirmed.

The present paper compares the effects of histamine and four histamine-like agonists on blood pressure in the cat. Prior to this study Black *et al.* (1972) had shown that 2-methylhistamine had greater potency on H_1-receptor systems than on H_2-receptor systems, whereas 4-methylhistamine was more effective on H_2-receptor systems than on H_1-receptor systems. The other two agonists, 2-(2-aminoethyl)pyridine and 2-(2-aminoethyl)thiazole, had both been shown to cause H_1-receptor effects only (Lee & Jones, 1949; Grossman *et al.*, 1952; Durant *et al.*, 1975).

Each of the agonists tested also caused dose-dependent depressor responses. Both 2-(2-aminoethyl)pyridine and 2-(2-aminoethyl)-thiazole caused depressor responses by interaction with H_1-receptors and even when given at doses as high as 1×10^{-5} mol/kg there was no evidence of interaction with H_2-receptors.

2-Methylhistamine interacted selectively with H_1-receptors when given in doses up to 1×10^{-7} mol/kg causing large depressor responses in the cat. It was evident, however, that doses larger than 1×10^{-7} mol/kg could interact with H_2-receptors. When these larger doses were given, in the presence of mepyramine, the depressor responses were reduced by H_2-receptor blockade with metiamide. The selective H_2-receptor agonist activity of 4-methylhistamine could only be confirmed at doses up to 1×10^{-7} mol/kg. Although doses up to 1×10^{-7} mol/kg lowered blood pressure the responses were less than the maximum which could be obtained with 4-methylhistamine in untreated cats. Doses of 4-methylhistamine in excess of 1×10^{-7} mol/kg lowered blood pressure by interaction with both H_1- and H_2-receptors. In untreated cats mepyramine alone did not alter the responses to the smaller doses of 4-methylhistamine whereas metiamide alone did. The displacement of the dose-response curve by metiamide alone was not very large. The responses which persisted in the presence of metiamide were due to interaction with H_1-receptors and they were reduced or abolished by mepyramine.

When the selectivity of the agonists had been established they were assayed for H_1- and H_2-receptor activity relative to histamine. The measured potencies, relative to histamine, for 2-methylhistamine and 4-methylhistamine were very similar to the values reported by Black *et al.* (1972) on non-cardiovascular histamine receptors and by Flynn & Owen (1975) on vascular histamine receptors. The assay figures for 2-(2-aminoethyl)pyridine and 2-(2-aminoethyl)-thiazole on blood pressure are also similar to the values determined by Flynn & Owen (1975) on vascular receptors. Although it is not possible to exclude other contributions to the depressor responses, dilatation of resistance vessels does appear to be a major cause of the depressor responses to bolus injection of histamine and histamine-like agonists.

The effects of histamine on the cardiovascular system are complex. Although both H_1- and H_2-receptors are involved in the gross blood pressure response to histamine it is possible that a detailed study of the component parts of the total response will reveal single receptor phenomena. Understanding of the parts of the total cardiovascular response has been greatly facilitated by the availability of both H_1- and H_2-receptor antagonists. In addition, the use of selective agonists will provide valuable backing to studies

with the selective antagonists. These experiments in cats indicate that either 2-(2-aminoethyl)-pyridine or 2-(2-aminoethyl)thiazole can be used as selective H_1-receptor agonists in the cardiovascular system. 2-Methylhistamine can also be used as a selective H_1-receptor agonist providing the doses used do not exceed 1×10^{-7} mol/kg since larger doses may also interact with H_2-receptors. 4-Methylhistamine may be used as a selective H_2-receptor agonist only at doses up to 1×10^{-7} mol/kg, which do not elicit maximum depressor responses in untreated cats.

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