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Cardiovascular studies with SK&F 93319, an antagonist of histamine at both H_1- and H_2-receptors

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1 Cardiovascular studies have been made in anaesthetized cats with SK&F 93319, an antagonist of histamine at both H_1- and H_2-receptors.

2 SK&F 93319, 8×10^{-8} and 4×10^{-7} mol kg^{-1} min^{-1} antagonized depressor responses to injections of histamine and the maximum displacement of histamine dose-response curves exceeded that which can be obtained with either an H_1-receptor antagonist or an H_2-receptor antagonist alone.

3 SK&F 93319, 8×10^{-8} and 4×10^{-7} mol kg^{-1} min^{-1}, also caused dose-dependent antagonism of histamine-induced falls in blood pressure and total peripheral resistance during intravenous infusions of histamine.

4 SK&F 93319 inhibited depressor responses to intravenous injections of 2-(2-aminoethyl)pyridine, dimaprit and impromidine. The displacement of the 2-(2-aminoethyl)pyridine dose-response curve was similar to the displacement of histamine dose-response curves. SK&F 93319 caused greater displacement of dimaprit or impromidine dose-response curves than of histamine or 2-(2-aminoethyl)pyridine dose-response curves.

5 SK&F 93319 was an effective antagonist of histamine, 2-(2-aminoethyl)pyridine or dimaprit-induced vasodilatation in femoral and gastric vasculature.

6 SK&F 93319 has been shown to be an effective antagonist of vascular responses to histamine in anaesthetized cats. SK&F 93319 appeared to be more effective as an H_2-receptor antagonist than as an H_1-receptor antagonist in these vascular studies.

Introduction

The first suggestion that histamine may elicit responses by interaction at more than one receptor site was made, after cardiovascular studies, by Folkow *et al.* (1948). Since selective histamine H_1- and H_2-receptor agonists and antagonists became available, there is now clear evidence that both H_1- and H_2-receptors are present in the peripheral circulation. Thus, substantial antagonism of depressor and vasodilator responses to histamine may be achieved only by simultaneous use of H_1- and H_2-receptor antagonists (Black *et al.*, 1972; 1975), and both H_1- and H_2-receptor agonists elicit depressor and vasodilator responses (e.g. Owen, 1975; Flynn & Owen, 1975; Flynn *et al.*, 1977; Owen *et al.*, 1979).

SK&F 93319 (Figure 1) is an antagonist of the actions of histamine at both H_1- and H_2-receptors (Blakemore *et al.*, 1983). It was therefore of particular interest to study the antagonism of cardiovascular actions of histamine by SK&F 93319. A preliminary account of some of these data has been presented to the British Pharmacological Society (Harvey & Owen, 1983).

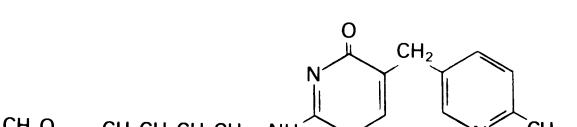

Figure 1 SK&F 93319.

Methods

Experiments were performed on cats of either sex, body weight 1.5–3.0 kg, anaesthetized by an intraperitoneal injection of sodium pentobarbitone, 60 mg kg^{-1}. Supplementary doses of sodium pentobarbitone were given, if necessary, to maintain anaesthesia. The trachea was cannulated.

Antagonism of depressor responses to histamine and histamine receptor agonists

The right femoral artery was cannulated to measure systemic blood pressure with a Statham P23A blood pressure transducer. Blood pressure was monitored on a Devices M8 electronic recorder. Drugs were administered via cannulae inserted into the right femoral and right brachial veins.

Antagonism of histamine-induced reductions in total peripheral resistance

One femoral artery was cannulated to measure blood pressure and heart rate was derived from the blood pressure pulse used to trigger an instantaneous heart rate meter. One femoral vein and one brachial vein were cannulated for administration of drugs. The chest was opened through a suitable intercostal space to give access to the ascending aorta, which was dissected free of surrounding tissue to allow tight placement of an electromagnetic flow probe (Statham/C-type with slide closure) around the vessel.

Histamine was administered by intravenous infusion at rates of 3.16×10^{-8} and 1×10^{-7} mol kg^{-1} min^{-1}. Each infusion was of 5 min duration with 10 min between infusions.

Antagonism of vasodilator responses to histamine and histamine receptor agonists in the cat femoral vasculature

Systemic blood pressure was measured from a cannula in the right common carotid artery connected to a Statham P23A blood pressure transducer and recorded on a Devices M8 electronic recorder. The left hind limb was acutely denervated by severing the sciatic nerve bundle in the popliteal cavity. The cat was given heparin 1000 iu kg^{-1}. The right femoral artery was cannulated and blood pumped through silicone rubber tubing by a Watson Marlow flow inducer at constant pulsatile flow into the left femoral artery. A small segment of thick rubber tubing was inserted into the external perfusion circuit before the pump for the injection of histamine and histamine receptor agonists. The perfusion pressure was measured by a blood pressure transducer from a side-arm in the perfusion circuit between the pump and the perfused hind-limb. At the start of experiments, the rate of flow was adjusted so that the perfusion pressure was approximately equal to systemic blood pressure and was kept constant at this rate for the duration of the experiment.

Antagonism of vasodilator responses to histamine in the cat gastric vasculature

The stomach was perfused via the coeliac artery (Harvey et al., 1980). Blood for perfusion of the stomach was withdrawn from one carotid artery. Blood flow distribution from the coeliac artery was restricted to the left gastric artery by ligation of other branches of the vascular bed; perfusion of the stomach by branches of the superior mesenteric artery was eliminated by a tight ligature placed around the pyloric end of the stomach.

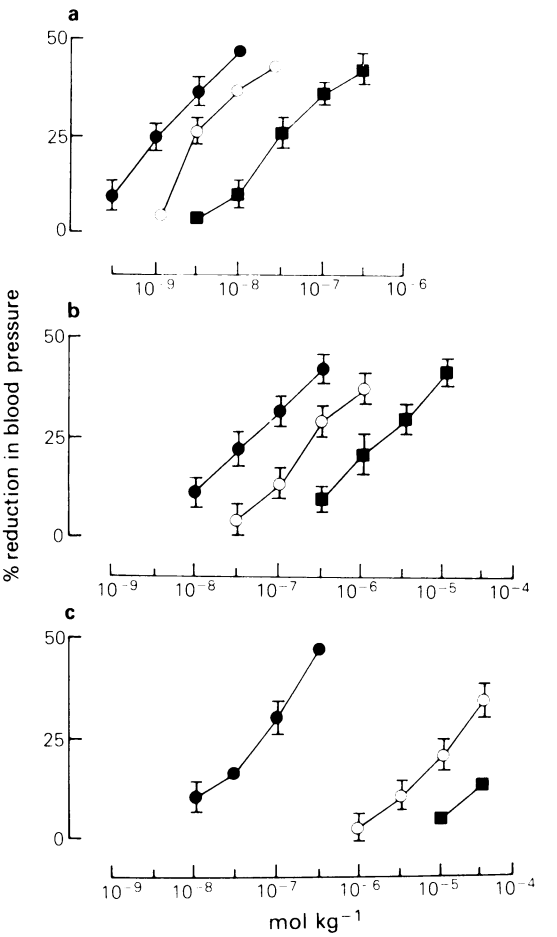

Figure 2 Antagonism of depressor responses to histamine (a), 2-(2-aminoethyl)pyridine (b) and dimaprit (c) by SK&F 93319. Control agonist dose-response curve (●), responses during the infusion of SK&F 93319, 8×10^{-8} mol kg^{-1} min^{-1} (○), responses during the infusion of SK&F 93319, 4×10^{-7} mol kg^{-1} min^{-1} (■). Points are mean of $n = 4$; s.e. indicated by vertical lines.

Table 1 Antagonism of depressor and vasodilator (femoral vasculature) responses to histamine and histamine receptor agonists by SK&F 93319

Dose of SK&F 93319 (mol kg^{-1} min^{-1})	*Mean dose-ratios* (95% confidence limits, $n = 4$) *Histamine*	*2-(2-Aminoethyl) pyridine*	*Dimaprit*	*Impromidine*
		Depressor responses		
1.6×10^{-8}	1.06 (1.02–1.1)	—	9.7 (9.2–10.3)	9.9 (9.4–10.5)
8×10^{-8}	3.4 (2.4–4.9)	5.5 (3.3–10.5)	200 (111–500)	—
4×10^{-7}	32.3 (19.2–52.6)	55.6 (9.6–500)	1190 (750–2270)	848 (286–2380)
		Vasodilator responses		
8×10^{-8}	2.8 (1.5–5.2)	5.3 (2.8–11.5)	526 (85–10000)	—
4×10^{-7}	47.6 (19.6–143)	53.5 (19.3–208)	4348 (1852–12500)	—

Histamine and histamine-like agonists were administered into the perfusion circuit for each vascular bed in a volume of 10 μl kg^{-1}.

Drugs

The following drugs were used: histamine acid phosphate (B.D.H.), 2-(2-aminoethyl)pyridine dihydrochloride, dimaprit dihydrochloride, impromidine trihydrochloride and SK&F 93319 trihydrochloride (all Smith Kline & French Research Ltd). All drugs were freshly prepared in 0.9% w/v sodium chloride solution.

Calculations

Analysis of variance was used to estimate the displacement of agonist dose-response curves by comparison of the potency of the agonist in the presence and absence of antagonist. The analysis was restricted to a 2 + 2 doses comparison over the range where response was linear with respect to log dose; a test for parallelism was incorporated into the programme.

Results

Depressor responses

SK&F 93319 antagonized depressor responses to histamine, 2-(2-aminoethyl)pyridine and dimaprit (Figure 2). Infusion of SK&F 93319, 8×10^{-8} and 4×10^{-7} mol kg^{-1} min^{-1}, caused parallel displacement to the right of the histamine and 2-(2-aminoethyl)pyridine dose-response curves with similar dose-ratios for both agonists (Table 1). Antagonism of the responses to the H_2-receptor agonist dimaprit occurred additionally at 1.6×10^{-8} mol kg^{-1} min^{-1} and greater dose-ratios were obtained for dimaprit than for histamine or 2-(2-aminoethyl)pyridine at any given dose of SK&F 93319 (Table 1). In a study comparing antagonism of depressor responses to histamine, dimaprit and impromidine, SK&F 93319, 1.6×10^{-8} mol kg^{-1} min^{-1} had no significant effect on the histamine dose-response curves but caused parallel displacement to the right for both the dimaprit and impromidine dose-response curves with similar dose-ratios for both agonists (Table 1).

Histamine-induced reductions in total peripheral resistance

Histamine lowers systemic arterial blood pressure by causing a reduction in total peripheral vascular resis-

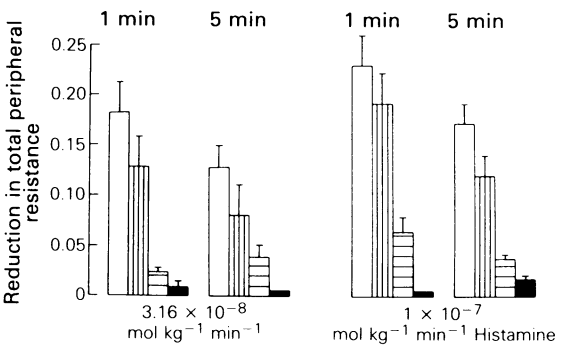

Figure 3 Histamine-induced reductions in total peripheral resistance units (mm Hg min ml^{-1}) and their antagonism by SK&F 93319. Histamine was infused at 3.16×10^{-8} or 1×10^{-7} mol kg^{-1} min^{-1}. The reduction in total peripheral resistance at the early peak response (1 min) and at the end of the infusion (5 min) are shown by the open columns. SK&F 93319, 8×10^{-8} (vertically hatched columns), 4×10^{-7} (horizontally hatched column), and 2×10^{-6} mol kg^{-1} min^{-1} (filled columns) reduced these responses. Values are means of $n = 4$; s.e. indicated by vertical lines.

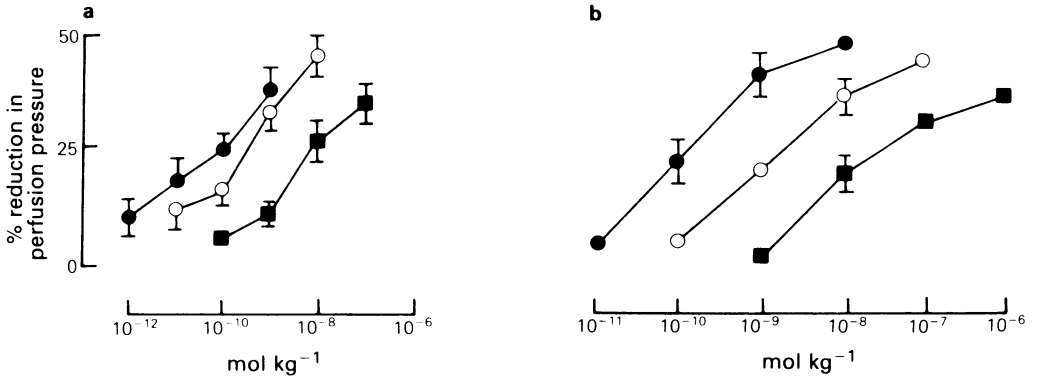

Figure 4 Antagonism of vasodilator responses to histamine by SK&F 93319. (a) Femoral vasculature: control dose-response curve (●); histamine during infusion of SK&F 93319, 8×10^{-8} mol kg^{-1} min^{-1} (○); histamine during infusion of SK&F 93319, 4×10^{-7} mol kg^{-1} min^{-1} (■). Values are mean of $n = 4$; s.e. indicated by vertical lines. (b) Gastric vasculature: control dose-response curve (●), histamine during the infusion of SK&F 93319, 1×10^{-8} mol kg^{-1} min^{-1} (○), histamine during the infusion of SK&F 93319, 1×10^{-7} mol kg^{-1} min^{-1} (■). Values are mean of $n = 4$; s.e. indicated by vertical lines.

tance (Owen *et al.*, 1982). SK&F 93319, 8×10^{-8}, 4×10^{-7} and 2×10^{-6} mol kg^{-1} min^{-1}, which had no significant effect on the resting haemodynamic parameters, caused dose-dependent reductions in this vasodilator response to histamine (Figure 3). The antagonist action of SK&F 93319 was evident both early in the infusion (after 1 min), when the response is due predominantly to action at H_1-receptors, and at the end of the infusion when the response is due predominantly to action at H_2-receptors (Owen *et al.*, 1982).

Vasodilator responses

SK&F 93319 inhibited vasodilator responses to histamine in both the femoral and gastric vasculature (Figure 4) causing dose-dependent displacement to the right of the histamine dose-response curves.

SK&F 93319 8×10^{-8} and 4×10^{-7} mol kg^{-1} min^{-1} also antagonized vasodilator responses to 2-(2- aminoethyl)pyridine and dimaprit in the femoral vasculature. As with antagonism of depressor responses, the displacement of dose-response curves was similar for histamine and 2-(2-aminoethyl)pyridine and substantially greater for dimaprit (Table 1).

Discussion

Intravenous injection or infusion of histamine lowers total peripheral vascular resistance and leads to reductions in arterial blood pressure. Histamine-like responses may be reproduced by administration of either an H_1-receptor agonist or an H_2-receptor agonist (e.g. Owen, 1975; Flynn *et al.*, 1975; Owen *et al.*, 1979) and responses to histamine can only be completely antagonized by simultaneous use of both H_1- and H_2-receptor antagonists (Black *et al.*, 1972; 1975).

SK&F 93319 is an antagonist of the actions of histamine at both H_1- and H_2-receptors. Thus, SK&F 93319 antagonizes the positive chronotropic action of histamine on the guinea-pig isolated atrium with a pA_2 value of 7.49 and inhibits the histamine-induced contractions of guinea-pig isolated ileum with a pA_2 value of 7.67 (Blakemore *et al.*, 1983).

SK&F 93319 antagonized the depressor responses to intravenous bolus injections of histamine. The displacement of the histamine dose-response curve achieved at the higher infusion rate of SK&F 93319, 4×10^{-7} mol kg^{-1} min^{-1}, dose-ratio of 32.3 (19.2–52.6, 95% confidence limits), exceeded the maximum displacement possible with an H_1-receptor antagonist alone e.g. mepyramine causes a maximal displacement with a dose-ratio of 8.6 (4.7–15.8), (Black *et al.*, 1975) and diphenylpyraline a dose-ratio of 9.6 (6.0–15.3) (Flynn, 1977). Histamine H_2-receptor antagonists do not displace the histamine dose-response curve following bolus injections of histamine (Black *et al.*, 1972; 1975; Flynn, 1977), although combination of an H_1-receptor antagonist and an H_2-receptor antagonist can displace histamine dose-response curves with dose-ratios in excess of 100. The extent of the antagonism of the histamine depressor responses by SK&F 93319 is thus consistent with its action as both an H_1- and H_2-receptor antagonist and indicated that activity at both receptors sites occurred at the doses used. Confirmation of the antagonist activity of SK&F 93319 at both recep-

tor sites was evident from the antagonism of depressor responses to both 2-(2-aminoethyl)pyridine, a relatively selective H_1-receptor agonist (Durant *et al.*, 1975) and dimaprit, a selective H_2-receptor agonist (Parsons *et al.*, 1977). The antagonism of dimaprit responses exceeded the antagonism of responses to 2-(2-aminoethyl)pyridine suggesting that the compound was more effective as an H_2-antagonist under the conditions of the current cardiovascular studies. The displacement of dose-response curves to dimaprit was similar to that for an alternative H_2-receptor agonist impromidine (Durant *et al.*, 1978), confirming the effectiveness of SK&F 93319 as an H_2-receptor antagonist in the cardiovascular system.

SK&F 93319 also antagonized the reduction in total peripheral resistance caused by intravenous infusion of histamine. The pharmacology of the vasodilator response to histamine infusions has been shown to have a time-base with a predominant role for H_1-receptors in the immediate peak response, within 1 min of the start of the intravenous infusion, which changes to a predominant role for H_2-receptors in the sustained response when infusions exceed 2 or 3 min. This time base was first observed by Chipman & Glover (1976) in human forearm and has now been found in a variety of vascular beds in different species including the peripheral vasculature in anaesthetized cats (Harvey & Owen, 1980; Owen *et al.*, 1982). SK&F 93319 was an effective antagonist of both the early and sustained vasodilator responses to histamine in the peripheral circulation, indicative of its antagonist activity at both H_1- and H_2-receptors on peripheral resistance vessels.

Further studies in the acutely denervated femoral vasculature (Flynn & Owen, 1975) and in the gastric vasculature (Harvey *et al.*, 1980) demonstrated that SK&F 93319 causes a greater displacement of histamine vasodilatation dose-response curves than can be achieved by either H_1- or H_2-receptor antagonists given alone. In the hind limb vascular bed, for example, mepyramine alone displaced the histamine dose-response curve with a maximum dose ratio of 10.1 (8.7–11.7, Flynn & Owen, 1975) compared with the significantly greater dose-ratio of 47.6 (19.6–143) achieved in the present studies. The studies in the femoral vasculature, like the studies on depressor responses, showed that SK&F 93319 caused greater displacement of dose-response curves to dimaprit than to 2-(2-aminoethyl)pyridine suggesting greater potency as an H_2-receptor than an H_1-receptor antagonist on histamine receptors in cat vasculature.

The reasons for the apparently greater potency of SK&F 93319 as an H_2-rather than H_1-receptor antagonist in these studies was unexpected because of the similar pA_2 values derived on classical H_1- and H_2-receptor systems *in vitro* (Blakemore *et al.*, 1983), and further study is needed to clarify the basis of this difference.

SK&F 93319 thus antagonizes the depressor and vasodilator responses to histamine and to either H_1- or H_2-receptor agonists. Even when administered at the high infusion rate of 2×10^{-6} mol kg^{-1} min^{-1} which essentially abolished the responses to the large doses of exogenous histamine used, there were no measurable changes in resting haemodynamic variables. The lack of measurable change in resting cardiovascular function following administration of SK&F 93319 provides further evidence that exogenous histamine has little or no role in control of normal haemodynamic function. This is similar to the lack of measureable haemodynamic change after administration of selective H_1- and H_2-receptor antagonists. The degree of antagonism of vascular responses to histamine by SK&F 93319 exceeds that possible with either an H_1- or H_2-receptor antagonist alone and can only be achieved by combined use of both types of antagonist. SK&F 93319 is thus likely to be a useful tool in the study of histamine and its pharmacology and may have therapeutic usefulness in conditions in which both types of antagonist may be used e.g. some inflammatory skin diseases such as the urticarias and mastocytosis.

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