Histamine-induced vasodilatation in the human forearm vasculature

Euan A. Sandilands,¹ Jane Crowe,² Hayley Cuthbert,² Paul J. Jenkins,³
Neil R. Johnston,⁴ Michael Eddleston,^{1,4} D. Nicholas Bateman¹ &
David J. Webb⁴

¹NPIS (Edinburgh), Scottish Poisons Information Bureau, Royal Infirmary of Edinburgh, Edinburgh,

²Wellcome Trust Clinical Research Facility, Royal Infirmary of Edinburgh, Edinburgh, ³Department of Orthopaedics, Royal Infirmary of Edinburgh, Edinburgh and ⁴Clinical Pharmacology Unit, University/BHF Centre for Cardiovascular Science, University of Edinburgh, The Queen's Medical Research Institute, Edinburgh, UK

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Histamine is an inflammatory mediator with potent vascular effects that include vasodilatation.
- H₁-receptors are responsible for many of the clinical effects in allergic disease.
- The additional benefit of H₂-receptor blockade in inhibiting histamine-induced vasodilatation is unclear.

WHAT THIS STUDY ADDS

- H₂-receptors are important in mediating histamine-induced vasodilatation and flare in human forearm resistance vessels.
- Histamine-induced vasodilatation does not appear to be subject to acute tolerance.
- Further research into the use of combined H₁- and H₂-receptor antagonist therapy should be considered in the treatment of acute allergic syndromes.

Correspondence

Dr Euan Sandilands, NPIS Edinburgh, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK.
Tel.: +44 131 242 1383
Fax: +44 131 242 1387
E-mail: euan.sandilands@luht.scot.nhs.uk

Keywords

forearm blood flow, histamine, vasodilatation, venous occlusion plethysmography

Received

19 June 2012

Accepted

22 February 2013

Accepted Article

Published Online

11 March 2013

AIM

To investigate the mechanism of action of intra-arterial histamine in the human forearm vasculature.

METHODS

Three studies were conducted to assess changes in forearm blood flow (FBF) using venous occlusion plethysmography in response to intra-brachial histamine. First, the dose–response was investigated by assessing FBF throughout a dose-escalating histamine infusion. Next, histamine was infused at a constant dose to assess acute tolerance. Finally, a four way, double-blind, randomized, placebo-controlled crossover study was conducted to assess FBF response to histamine in the presence of H₁- and H₂-receptor antagonists. Flare and itch were assessed in all studies.

RESULTS

Histamine caused a dose-dependent increase in FBF, greatest with the highest dose (30 nmol min⁻¹) infused [mean (SEM) infused arm vs. control: 26.8 (5.3) vs. 2.6 ml min⁻¹ 100 ml⁻¹; $P < 0.0001$]. Dose-dependent flare and itch were demonstrated. Acute tolerance was not observed, with an increased FBF persisting throughout the infusion period. H₂-receptor antagonism significantly reduced FBF (mean (95% CI) difference from placebo at 30 nmol min⁻¹ histamine: −11.9 ml min⁻¹ 100 ml⁻¹ (−4.0, −19.8), $P < 0.0001$) and flare (mean (95% CI) difference from placebo: −403.7 cm² (−231.4, 576.0), $P < 0.0001$). No reduction in FBF or flare was observed in response to the H₁-receptor antagonist. Itch was unaffected by the treatments. Histamine did not stimulate vascular release of tissue plasminogen activator or von Willebrand factor.

CONCLUSION

Histamine causes dose-dependent vasodilatation, flare and itch in the human forearm. H₂-receptors are important in this process. Our results support further exploration of combined H₁- and H₂-receptor antagonist therapy in acute allergic syndromes.

Introduction

Histamine is an important inflammatory mediator with potent vascular effects. It is well recognized for its role in anaphylaxis where, on re-exposure to an allergen, cross-linking of cell surface IgE stimulates mast cell degranulation and release of mediators, including histamine, resulting in vasodilatation and hypotension [1]. A similar role has been proposed in anaphylactoid reactions, although the mechanism of histamine release is less clear [2, 3].

The effect of histamine on vascular beds has been studied since the early 1900s. Four major sub-types of histamine receptor have been identified, with H_1 - and H_2 -receptors more widely expressed than H_3 - and H_4 -receptors [4]. While H_1 -receptors are responsible for most of the clinical effects in allergic disease [4–6], both H_1 - and H_2 -receptors are important mediators of histamine-induced vascular effects [7–10]. Animal studies have demonstrated that H_1 - and H_2 -receptor blockade attenuates histamine-induced vasodilatation with the greatest effect following combined antagonist administration [7, 11, 12]. Studies of coronary vessels in dogs have demonstrated H_1 -mediated vasoconstriction and H_2 -mediated vasodilatation of proximal coronary vessels, but both H_1 - and H_2 -mediated vasodilatation in distal vessels [13, 14]. Duff *et al.* performed some of the earliest human studies using venous occlusion plethysmography to measure forearm blood flow (FBF) in response to intra-arterial (i.a.) histamine [15]. Marked vasodilatation was demonstrated and this was attenuated by a first generation H_1 -receptor antagonist [16]. Chipman & Glover [17] demonstrated with the same methodology, but using a less selective H_2 -receptor antagonist, an important role for H_2 -receptors, as well as H_1 -receptors, in histamine induced vasodilatation. Subsequent human studies explored the effect of histamine in other vascular beds [8, 9, 18–22], but no further studies investigating the effect of i.a. histamine on human forearm resistance vessels in the presence of newer selective histamine antagonists have been performed.

Histamine may also play an important role in the release of tissue plasminogen activator (t-PA) and von Willebrand factor (vWF). Histamine treatment of human umbilical vein endothelial cells (HUVECs) *in vitro* causes release of t-PA and vWF that is inhibited by H_1 - but not H_2 -receptor antagonists [23–25]. Histamine-induced t-PA release has also been demonstrated in perfused vascular preparations and *in vivo* in animals [26, 27]. While histamine-induced t-PA release has not been studied in humans, i.v. infusion of histamine has been shown to cause secretion of vWF in healthy volunteers [28].

Our aim was to build on earlier work [15, 16] to investigate further the mechanism of histamine-induced vasodilatation in the human forearm resistance vessels using venous occlusion plethysmography, and

additionally, to explore the role of histamine in vWF and t-PA release in this vascular bed.

Methods

Subjects

The study was undertaken in healthy men aged between 20 and 50 years. Written informed consent was obtained from each subject prior to the study, which was approved by the local research ethics committee. Volunteers were required to be non-smokers with no documented history of vascular disease (hypertension, diabetes, hypercholesterolaemia), asthma, atopy, and to not be taking any regular medication. It was requested that volunteers fasted from midnight before the study, abstained from caffeine-containing drinks and alcohol on the study day, and avoided any antihistamine preparations in the 2 weeks prior to the study.

Drugs

All drugs were supplied by the pharmacy department of the Royal Infirmary of Edinburgh. Histamine diphosphate (Tayside Pharmaceuticals, UK) was used in study 1. Due to supply limitations of this preparation, equivalent molar doses of histamine dihydrochloride (Meda Pharmaceuticals Ltd, New Jersey, USA) were used in studies 2 and 3. Co-infusions of an H_1 -receptor antagonist (chlorphenamine maleate, Archimedes Pharma UK Ltd) and an H_2 -receptor antagonist (ranitidine, GlaxoSmithKline UK) were administered in study 3.

An initial exploratory study in a single subject was carried out to investigate the vasodilatory response to i.a. histamine in the forearm. After baseline measurements, i.a. histamine was administered at doses of 0.75, 3, 12, 24, 48 and 96 nmol min⁻¹ each for 10 min. These doses were based on those used safely and effectively in the past [16]. While vasodilatation was demonstrated in the infused arm, at higher doses (48 and 96 nmol min⁻¹) FBF also increased in the non-infused arm. Concurrently, a substantial and discomforting flare reaction in the infused arm was observed and the volunteer reported a headache, indicating a systemic effect. Following discussion with the ethics committee, the protocol was refined to 0.09, 0.3, 0.9, 3, 9, 30 nmol min⁻¹ histamine.

H_1 - and H_2 -receptor antagonist doses were calculated to achieve plasma concentrations approximately equivalent to those following therapeutic intravenous (i.v.) administration. Plasma concentrations of 8–16 µg l⁻¹ have been observed following therapeutic i.v. administration of 8 mg chlorphenamine maleate (volume of distribution 1–10 l kg⁻¹) [29]. Assuming a forearm blood flow of 50 ml min⁻¹ [30], i.a. administration of 1 µg min⁻¹ would be expected to achieve a similar plasma concentration (~20 µg l⁻¹). Therapeutic concentrations of 150 µg l⁻¹ ranitidine have been demonstrated following a standard i.v.

dose of 50 mg (volume of distribution 1–2 l kg⁻¹) [29]. I.a. administration of 7.5 µg min⁻¹ would therefore be expected to achieve similar forearm concentrations, assuming a forearm blood flow of 50 ml min⁻¹.

Histamine has been shown to result in a three-fold increase in FBF [16]. To ensure maximal receptor blockade even in the presence of histamine, five-fold higher doses of H₁-receptor antagonist (5 µg min⁻¹) and H₂-receptor antagonist (37.5 µg min⁻¹) were then infused during a second dose-escalating i.a. histamine infusion.

Forearm blood flow measurement

Studies were conducted, after a 30 min period of rest, in volunteers resting supine in a quiet, temperature-controlled environment (23–25°C). At the start of each study the brachial artery of the non-dominant arm was cannulated with a 27-gauge cannula (Cooper's Needle Works Ltd, UK) under local anaesthetic (2% lignocaine, Hameln Pharmaceuticals Ltd, UK) and connected to an Asena GH infusion pump (Alaris Medical Systems, UK) via a 16-gauge epidural catheter (Smiths Medical International Ltd, UK). The i.a. infusion was maintained throughout all studies at 1 ml min⁻¹.

FBF was measured by venous occlusion plethysmography as previously described [30]. Mercury-in-silastic strain gauges were applied around the widest part of both infused and non-infused forearms, allowing the latter to act as a control for any systemic effect of drug infusion. The hands were excluded through inflation of wrist cuffs to 200 mmHg. FBF recordings were made during the final 3 min of each drug infusion interval. Cuffs placed around the upper arm were intermittently inflated to 40 mmHg for the first 9 in every 12 s throughout each 3 min measurement period, temporarily preventing venous outflow and allowing plethysmography recordings. The mean of the final five measurements (expressed as ml min⁻¹ 100 ml⁻¹ forearm volume) was used for analysis. Blood pressure and pulse were measured following each FBF measurement in the non-infused arm with an appropriate sized cuff, by use of a validated oscillometric sphygmomanometer (P.M.S (Instruments) Ltd, Hokanson, UK).

Assays

Blood samples were obtained for assay of histamine, vWF, and t-PA from the deep veins in both arms during each histamine dose. Histamine was measured following an initial conversion to the acylated form and subsequent competitive enzyme linked immunosorbent assay (ELISA) using a commercially available kit (IBL, Hamburg, Germany). Histamine concentrations are reported in ng ml⁻¹. von Willebrand factor was measured using the REAADS® von Willebrand Factor Antigen (vWF:Ag) Test Kit (Corgenix UK Ltd, Peterborough, UK), an ELISA that determines vWF levels in human plasma, expressed as patient vWF : Antigen percentage (%) concentration when determined against a reference plasma standard. t-PA antigen

and activity were determined using the t-PA Combi Actibind ELISA Kit (Technoclone GmbH, Vienna, Austria) that allows combined quantitative determination of concentration and activity of t-PA using a single plate assay. t-PA antigen concentration and activity are reported as ng ml⁻¹ and IU ml⁻¹, respectively.

Skin response

A flare response was observed during the i.a. histamine infusion. Accurate quantification of the area of flare was challenging, as it varied in shape and time. Total area was estimated by multiplying the width by the length of the erythematous area, assuming it to be symmetrical. Although this tended to overestimate flare area, this method was used by the same investigator throughout all studies maintaining consistency. Volunteers were also asked to record itch subjectively on a scale of 1 (no itch) to 7 (intense itch) during each histamine dose infused [31].

Study protocol

Study 1: Dose-response study Six volunteers received an i.a. incremental dose infusion of histamine (0.09, 0.3, 0.9, 3, 9, 30 nmol min⁻¹). Each dose was infused for 10 min with no washout between doses, and followed by a 30 min washout period at the end of the study. Blood samples were obtained for assay of histamine, vWF and t-PA from the deep veins in both arms during each histamine dose.

Study 2: Acute tolerance study Following demonstration of dose-dependent vasodilatation, acute tolerance was investigated by assessing FBF measurements during a 1 h continuous infusion of 5 nmol min⁻¹ histamine in six volunteers. As in study 1, FBF measurements and blood samples were taken every 10 min during the infusion.

Study 3: Mechanistic study Study 3 was a four way, double-blind, randomized, placebo-controlled crossover study addressing the mechanism of histamine-induced forearm responses. Six volunteers were each requested to attend on four separate occasions. During each visit volunteers received a dose-escalating i.a. infusion of histamine similar to that used in study 1 but with a simplified regimen of four doses (0.16, 0.9, 5, 30 nmol min⁻¹). Volunteers were randomized to receive an additional i.a. co-infusion of one of four treatments during each visit: saline (placebo), H₁-receptor antagonist, H₂-receptor antagonist, or a combination of H₁- and H₂-receptor antagonists. Following a 20 min washout period the i.a. histamine infusion was repeated in the presence of a higher dose of the co-infused antagonist/placebo. The study was completed with a 30 min washout period. While the histamine infusion was not blinded, both the subject and investigator were blind to the specific co-infusion being administered on each visit, minimizing any bias in

Table 1

Volunteer demographic and baseline data. Results are presented as mean (SEM). BMI, body mass index; FBF, forearm blood flow (expressed as ml min⁻¹ 100 ml⁻¹ forearm volume)

	Study 1 Mean (SEM)	Study 2 Mean (SEM)	Study 3 Mean (SEM)
<i>n</i>	6	6	6
Age (years)	29 (3)	32 (3)	28 (3)
BMI (kg m ⁻²)	24 (1)	25 (1)	24 (1)
Baseline systolic BP (mmHg)	144 (7)	134 (7)	129 (2)
Baseline diastolic BP (mmHg)	79 (4)	75 (3)	74 (1)
Baseline heart rate (beats min ⁻¹)	74 (4)	60 (4)	61 (2)
Baseline FBF infused arm	2.4 (0.5)	2.8 (0.5)	2.6 (0.2)
Baseline FBF control arm	2.0 (0.4)	2.5 (0.6)	2.7 (0.2)

the measurement of flare or interpretation of itch. Blood samples were obtained for assay of histamine and vWF during each histamine dose.

Statistical analysis

For studies 1 and 2, FBF measurements in the infused arm were compared with those in the non-infused arm using two-way analysis of variance (ANOVA) for repeated measures. At each drug dose (study 1) and time point (study 2) comparison was made with baseline FBF and non-infused FBF using paired two-tailed *t*-tests. For study 3, the FBF measurements in the infused arm for each treatment were compared using two way ANOVA for repeated measures. Where significant treatment effects were observed, analysis for each intervention was carried out using a *t*-test with Bonferroni correction for multiple comparisons.

Results

Six healthy male volunteers were recruited to and completed each study. Volunteers were allowed to participate in more than one study providing more than 2 weeks had passed between visits. The volunteers' characteristics are summarized in Table 1.

Study 1: Dose-response study

Baseline FBF measurements were similar between the infused and non-infused arms. The incremental histamine infusion led to a significant increase in FBF in the infused arm compared with the non-infused arm ($P = 0.004$) (Figure 1A). Further analysis demonstrated that FBF was significantly elevated at 3 nmol min⁻¹ [mean 10.3 (SEM 2.3) ml min⁻¹ 100 ml⁻¹, $P < 0.05$], rising to a maximum FBF during the highest histamine dose (30 nmol min⁻¹) infused [26.8 (5.3) ml min⁻¹ 100 ml⁻¹, $P < 0.0001$]. There was no significant change in BP, pulse or FBF in the non-infused arm and no headache reported, confirming that the effects

Figure 1

(A) FBF in response to an i.a. histamine infusion. ■ infused arm; □ control arm. (B) Flare and itch associated with an i.a. histamine infusion. □ flare; ○ itch

were confined to the infused arm. Measureable skin effects were observed at 3 nmol min⁻¹, with maximum flare and itch coinciding with the top histamine dose infused (Figure 1B). All these effects resolved following discontinuation of i.a. histamine with complete resolution by 30 min post-infusion.

Plasma concentration of histamine in the infused forearm was observed to increase in proportion to the dose-escalating infusion of histamine [mean (SEM) plasma histamine concentration (ng ml⁻¹) at baseline vs. histamine 30 nmol min⁻¹: 0.34 (0.04) vs. 17.59 (4.79), $P = 0.005$, Table 2]. No increase was observed in the non-infused arm

Table 2

Plasma measurements taken from the infused and non-infused arm during the i.a. histamine infusion in study 1. Results are expressed as mean (SEM). * $P = 0.005$; mean (SEM) plasma histamine concentration (ng ml^{-1}) during 30 nmol min^{-1} histamine infusion vs. baseline

	Baseline	Histamine 3 nmol min^{-1}	Histamine 30 nmol min^{-1}
Histamine (ng ml^{-1})			
Infused	0.34 (0.04)	1.42 (0.33)	17.59 (4.79)*
Non-infused	0.37 (0.04)	0.37 (0.03)	0.46 (0.07)
vWF (%)			
Infused	121.74 (18.5)	136.06 (19.2)	129.22 (13.8)
Non-infused	115.40 (11.2)	114.14 (12.6)	133.26 (16.5)
t-PA antigen (ng ml^{-1})			
Infused	2.99 (0.4)	2.99 (0.5)	3.86 (0.5)
Non-infused	3.26 (0.6)	2.79 (0.7)	2.89 (0.6)
t-PA activity (IU ml^{-1})			
Infused	0	0.02 (0)	0.1 (0.08)
Non-infused	0.01 (0)	0.01 (0)	0.03 (0.01)

confirming that the infused histamine did not reach the systemic circulation in concentrations that had measurable effects. No significant changes in plasma concentration of vWF or t-PA were observed in response to i.a. histamine.

Study 2: Acute tolerance study

Baseline FBF measurements were similar between the infused and non-infused arms. Infusion of 5 nmol min^{-1} histamine caused a significant increase in FBF [$12.6 (2.2) \text{ ml min}^{-1} 100 \text{ ml}^{-1}$, $P < 0.0001$, Figure 2A]. This persisted throughout the 60 min infusion period before returning towards baseline following termination of the histamine infusion. The flare response also failed to demonstrate acute tolerance (Figure 2B). In contrast, itch reduced over time. Plasma concentration of histamine in the infused arm increased and remained elevated throughout the i.a. infusion of histamine (Table 2). However, as in study 1, no significant change was observed in the concentration of vWF or t-PA.

Study 3: Mechanistic study

As in study 1, FBF increased in response to i.a. histamine. A significant reduction in FBF was observed when the H_2 -receptor antagonist was infused at both the lower and higher dose [lower dose: mean (95% CI) difference from placebo at 30 nmol min^{-1} histamine: $-11.9 \text{ ml min}^{-1} 100 \text{ ml}^{-1}$ ($-4.0, -19.8$), $P < 0.0001$; higher dose: $-9.7 \text{ ml min}^{-1} 100 \text{ ml}^{-1}$ ($-3.4, -16.0$), $P < 0.001$] (Figure 3). FBF was reduced in response to the H_1 -receptor antagonist although this reduction did not reach statistical significance even when infused at the higher dose. Combined H_1 - and H_2 -receptor blockade did not offer any additional benefit over the H_2 -receptor antagonist alone except

Figure 2

(A) Study of acute tolerance to i.a. histamine. ■ infused arm; □ control arm. (B) Flare and itch associated with the continuous infusion of i.a. histamine. □ flare; ○ itch

when both were infused at the higher dose [mean (95% CI) difference from placebo at 30 nmol min^{-1} histamine: $-13.6 (-7.3, -19.9)$, $P < 0.0001$] (Figure 3).

Flare response differed significantly between treatments, particularly during the higher dose antagonist infusions ($P < 0.0001$) (Figure 3). While the H_1 -receptor antagonist had no significant effect on flare, the H_2 -receptor antagonist significantly reduced flare when infused at the higher dose [mean (95% CI) difference from placebo, $-403.7 \text{ cm}^2 (-231.4, -576.0)$, $P < 0.0001$]. Combined H_1 - and H_2 -receptor antagonist treatment offered no additional effect over that seen with the H_2 -receptor antagonist alone. Itch was not significantly affected by any of the treatments administered.

Figure 3

FBF, flare and itch in the presence of histamine and histamine antagonists/placebo. ● placebo; ■ H₁-receptor antagonist; ◆ H₂-receptor antagonist; ▲ H₁- and H₂-receptor antagonist

As in study 1, plasma concentration of histamine in the infused forearm increased in proportion to the i.a. histamine infusion (Table 2). However, no significant change in vWF concentration was observed in response to i.a. histamine with or without the presence of a histamine antagonist.

Discussion

Our results confirm that histamine causes dose-dependent vasodilatation in the human forearm and show for the first time that this is not subject to acute tolerance. Dose-dependent flare and itch were also observed, and while flare similarly failed to demonstrate tolerance, itch did

reduce over time. A significant reduction in FBF was observed in response to the H₂-receptor antagonist, an effect not demonstrated following H₁-receptor blockade. H₂-receptor antagonism also brought about the greatest reduction in flare. Histamine did not stimulate vascular release of t-PA or vWF in this model.

Our antagonist studies suggest histamine does not regulate basal vascular tone. However, the results highlight a role for H₂-receptors in histamine-mediated vascular effects in arterial resistance vessels, important in the regulation of blood pressure during allergic reactions following histamine release. Previous healthy volunteer studies have supported a role for both H₁- and H₂-receptors in mediating histamine-induced dose-dependent venodilatation in the hands [8], vasodilation in the skin microcirculation [9] and systemic responses including a rise in pulse rate, fall in diastolic blood pressure and cutaneous flush [18]. In the eye [20,21] and coronary vasculature [19], however, H₁-, but not H₂-receptors, appear to be important in mediating histamine-induced vasodilatation.

Forearm venous occlusion plethysmography with local brachial artery infusion is considered a 'gold-standard' method in the assessment of human vascular function [30]. This robust, minimally invasive technique allows administration of drugs at subsystemic doses, therefore reducing the risk of unwanted systemic effects. Our study investigated healthy volunteers and this model does not therefore truly reflect anaphylaxis *in vivo*, where multiple other mediators and histamine receptors may be involved. Nevertheless, it does allow investigation of underlying mechanisms in a safe and controlled manner and potentially provides useful information that may guide future clinical trials. A novel finding in our study was the lack of acute tolerance to i.a. histamine. Whether tolerance would develop beyond 60 min remains unclear as it was not practicable to investigate this using this methodology. This does not diminish from the importance of this finding, however, in the context of acute allergic reactions such as anaphylaxis.

In contrast to the H₂-effect, our study demonstrated a small, although statistically insignificant, reduction in FBF in response to the H₁-antagonist. While this may reflect inadequate power to detect a significant change in FBF in response to H₁-receptor antagonism, a clear response was demonstrated with the H₂-receptor antagonist. Insufficient doses of the H₁-receptor antagonist may have been used. However, antagonist doses were calculated in precisely the same manner to achieve a local forearm concentration similar to the plasma concentration following therapeutic i.v. administration and a clear clinical response from H₂-receptor blockade was observed. Finally, it is possible that histamine receptors, other than those studied here, may be involved in mediating the clinical effects described. Recent animal studies show that H₃-receptors may be important in mediating endothelium dependent vasodilatation [32]. Also, activation of H₁- and

H₄-receptors, together with inhibition of H₃-receptors, are involved in eliciting histamine-induced itch [33, 34]. This may be important when considering the mechanism of tolerance observed to histamine-induced itch that was not observed for vasodilatation or flare. Lack of an effect from the H₁-receptor antagonist, however, does not diminish the significance of our results in highlighting an important role for H₂-receptors in histamine-induced vascular effects.

Flare reaction was subjectively quantified by multiplying the width by the length of the erythematous area. This process was necessarily minimally invasive in order to reduce interference with the arterial needle and strain gauges. The same observer, who, like the volunteer was blind to treatment, estimated flare area throughout all studies minimizing observer bias. While it is possible that the flare reaction itself could have altered FBF measurements, we feel that this is unlikely to have had any significant effect on the measurements. Changes in FBF were also noted before the flare appeared. While the assessment of itch was subjective, volunteers were blinded to each treatment they received minimizing any bias that may have affected interpretation.

In summary, histamine causes dose-dependent vasodilatation in man and it is likely that both H₁- and H₂-receptors are important in this process. While use of H₁-receptor antagonists in acute allergic syndromes is commonplace, addition of an H₂-receptor antagonist may provide greater blockade of histamine-induced vasodilatation and diminish the cutaneous features. Some animal [35] and human studies [36], however, have suggested that H₂-receptor blockade may potentially exacerbate coronary vasospasm with implications for their use in the treatment of anaphylaxis. Further work is needed to explore whether the addition of H₂-receptor antagonists would provide symptomatic benefit without inducing coronary ischaemia. Indeed, Lin *et al.* [37] conducted a randomized controlled trial in patients presenting with acute allergic syndromes to assess whether combined H₁- and H₂-receptor blockade, rather than H₁-receptor blockade alone, improved outcome. They concluded that combination therapy offered a significantly more rapid resolution of the cutaneous features of acute allergy but, as only two out of 91 patients demonstrated hypotension, any additional benefit of H₂-receptor antagonism in reversing hypotension, a feature associated with more severe allergic reactions, remained unclear. A combined approach may also be crucial in the treatment of anaphylactoid reactions where histamine also seems to play a pathophysiological role.

In conclusion we have shown in a well characterized human vascular resistance model that H₂-receptors play a key role in causing histamine-induced vasodilatation. These results seem likely to have relevance to the management of both allergic and non-allergic mediated adverse reactions in man that involve histamine release.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

We are grateful for the use of the facilities of the Wellcome Trust Clinical Research Facility, Royal Infirmary of Edinburgh, and the assistance of the nursing staff in the running of the study.

Contributors

The original idea for the study came from DJW. DJW, ME, DNB and EAS designed the studies. EAS undertook the work and wrote the manuscript. All authors reviewed the manuscript and are guarantors for the paper.

Ethical approval

The study protocol was approved by the local research ethics committee.

Funding

The study was funded by endowments within the Clinical Pharmacology Unit, University/BHF Centre for Cardiovascular Science, University of Edinburgh, and the NPIS (Edinburgh), Scottish Poisons Information Bureau, Royal Infirmary of Edinburgh.

REFERENCES

- 1 Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr, Bock SA, Branum A, Brown SGA, Carmago CA, Cydulka R, Galli SJ, Gidudu J, Gruchalla RS, Harlor AD, Hepner DL, Lewis LM, Lieberman PL, Metcalfe DD, O'Conner R, Muraro A, Rudman A, Schmitt C, Scherrer D, Simons FER, Thomas S, Wood JP, Decker WW. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; 117: 391–7.
- 2 Bateman DN, Woodhouse KW, Rawlins MD. Adverse reactions to N-acetylcysteine. *Hum Toxicol* 1984; 3: 393–8.
- 3 Waring WS, Stephen AF, Robinson OD, Dow MA, Pettie JM. Lower incidence of anaphylactoid reactions to

- N-acetylcysteine in patients with high acetaminophen concentrations after overdose. *Clin Toxicol (Phila)* 2008; 46: 496–500.
- 4** Simons FE. Advances in H₁-antihistamines. *N Engl J Med* 2004; 351: 2203–17.
- 5** MacGlashan D, Jr. Histamine: a mediator of inflammation. *J Allergy Clin Immunol* 2003; 112: (4 Suppl.): S53–9.
- 6** Akdis CA, Blaser K. Histamine in the immune regulation of allergic inflammation. *J Allergy Clin Immunol* 2003; 112: 15–22.
- 7** Black JW, Owen DA, Parsons ME. An analysis of the depressor responses to histamine in the cat and dog: involvement of both H₁- and H₂-receptors. *Br J Pharmacol* 1975; 54: 319–24.
- 8** Dachman WD, Bedarida G, Blaschke TF, Hoffman BB. Histamine-induced venodilation in human beings involves both H₁ and H₂ receptor subtypes. *J Allergy Clin Immunol* 1994; 93: 606–14.
- 9** Grossmann M, Jamieson MJ, Kirch W. Histamine response and local cooling in the human skin: involvement of H₁- and H₂-receptors. *Br J Clin Pharmacol* 1999; 48: 216–22.
- 10** Spitaler MM, Hammer A, Malli R, Graier WF. Functional analysis of histamine receptor subtypes involved in endothelium-mediated relaxation of the human uterine artery. *Clin Exp Pharmacol Physiol* 2002; 29: 711–6.
- 11** Toda N. Mechanism underlying responses to histamine of isolated monkey and human cerebral arteries. *Am J Physiol* 1990; 258: (2 Pt 2): H311–7.
- 12** Flynn SB, Owen DA. Histamine receptors in peripheral vascular beds in the cat. *Br J Pharmacol* 1975; 55: 181–8.
- 13** Pelc LR, Christensen CW, Gross GJ, Warltier DC. Direct cardiac actions of the H₂ receptor agonists, impromidine and dimaprit. *Eur J Pharmacol* 1985; 107: 379–84.
- 14** Miller WL, Bove AA. Differential H₁- and H₂-receptor-mediated histamine responses of canine epicardial conductance and distal resistance coronary vessels. *Circ Res* 1988; 62: 226–32.
- 15** Duff F, Greenfield AD, Shepherd JT, Thompson ID. A quantitative study of the response to acetylcholine and histamine of the blood vessels of the human hand and forearm. *J Physiol* 1953; 120: 160–70.
- 16** Duff F, Whelan RF. The effects of antihistamine substances on the response to histamine of the blood vessels of the human forearm. *Br J Pharmacol Chemother* 1954; 9: 413–8.
- 17** Chipman P, Glover WE. Histamine H₂-receptors in the human peripheral circulation. *Br J Pharmacol* 1976; 56: 494–6.
- 18** Kaliner M, Sigler R, Summers R, Shelhamer JH. Effects of infused histamine: analysis of the effects of H-1 and H-2 histamine receptor antagonists on cardiovascular and pulmonary responses. *J Allergy Clin Immunol* 1981; 68: 365–71.
- 19** Vigorito C, Giordano A, De Caprio L, Vitale DF, Maurea N, Silvestri P, Tuccillo B, Ferrara N, Marone G, Rengo F. Effects of histamine on coronary hemodynamics in humans: role of H₁ and H₂ receptors. *J Am Coll Cardiol* 1987; 10: 1207–13.
- 20** Resch H, Zawinka C, Lung S, Weigert G, Schmetterer L, Garhofer G. Effect of histamine and cimetidine on retinal and choroidal blood flow in humans. *Am J Physiol Regul Integr Comp Physiol* 2005; 289: R1387–91.
- 21** Weigert G, Zawinka C, Resch H, Schmetterer L, Garhofer G. Intravenous administration of diphenhydramine reduces histamine-induced vasodilator effects in the retina and choroid. *Invest Ophthalmol Vis Sci* 2006; 47: 1096–100.
- 22** McCord JL, Beasley JM, Halliwill JR. H₂-receptor-mediated vasodilation contributes to postexercise hypotension. *J Appl Physiol* 2006; 100: 67–75.
- 23** Hamilton KK, Sims PJ. Changes in cytosolic Ca²⁺ associated with von Willebrand factor release in human endothelial cells exposed to histamine. Study of microcarrier cell monolayers using the fluorescent probe indo-1. *J Clin Invest* 1987; 79: 600–8.
- 24** Levin EG, Santell L. Stimulation and desensitization of tissue plasminogen activator release from human endothelial cells. *J Biol Chem* 1988; 263: 9360–5.
- 25** Knop M, Aaeskjold E, Bode G, Gerke V. Rab3D and annexin A2 play a role in regulated secretion of vWF, but not tPA, from endothelial cells. *EMBO J* 2004; 23: 2982–92.
- 26** Smith D, Gilbert M, Owen WG. Tissue plasminogen activator release *in vivo* in response to vasoactive agents. *Blood* 1985; 66: 835–9.
- 27** Klocking HP, Markwardt F. Pharmacological stimulation of t-PA release. *Pharmazie* 1994; 49: 227–30.
- 28** Jilma B, Pernerstorfer T, Dirnberger E, Stohlawetz P, Schmetterer L, Singer EA, Grasselli U, Eichler HG, Kapiotis S. Effects of histamine and nitric oxide synthase inhibition on plasma levels of von Willebrand factor antigen. *J Lab Clin Med* 1998; 131: 151–6.
- 29** Dollery CBA, Burley D, Margerison Davies D, Davies D, Harrison P. *Therapeutic Drugs*, 1st edn. Edinburgh: Churchill Livingstone, 1991.
- 30** Wilkinson IB, Webb DJ. Venous occlusion plethysmography in cardiovascular research: methodology and clinical applications. *Br J Clin Pharmacol* 2001; 52: 631–46.
- 31** Spector SL, Nicklas RA, Chapman JA, Bernstein IL, Berger WE, Blessing-Moore J, Dykewicz MS, Fineman SM, Lee RE, Li JT, Portnoy JM, Schuller DE, Lang D, Tilles SA. Symptom severity assessment of allergic rhinitis: part 1. *Ann Allergy Asthma Immunol* 2003; 91: 105–14.
- 32** Sun P, Jin X, Koyama T, Li S, Kitamura Y, Kawasaki H. R-(–)-alpha-methylhistamine, a histamine H₃ receptor agonist, induces endothelium-dependent vasodilation in rat mesenteric resistance arteries. *Biol Pharm Bull* 2010; 33: 58–63.
- 33** Rossbach K, Nassenstein C, Gschwandtner M, Schnell D, Sander K, Seifert R, Stark H, Kietzmann M, Baumer W. Histamine H₁, H₃ and H₄ receptors are involved in pruritus. *Neuroscience* 2011; 190: 89–102.

- 34** Sugimoto Y, Iba Y, Nakamura Y, Kayasuga R, Kamei C. Pruritus-associated response mediated by cutaneous histamine H₃ receptors. *Clin Exp Allergy* 2004; 34: 456–9.
- 35** Felix SB, Baumann G, Niemczyk M, Hashemi T, Ochsenfeld G, Ahmad Z, Shirani S, Blomer H. Effects of histamine H₁- and H₂-receptor antagonists on cardiovascular function during systemic anaphylaxis in guinea pigs. *Agents Actions* 1991; 32: 245–52.
- 36** Shimokawa H, Okamatsu S, Taira Y, Nakamura M. Cimetidine induces coronary artery spasm in patients with vasospastic angina. *Can J Cardiol* 1987; 3: 177–82.
- 37** Lin RY, Curry A, Pesola GR, Knight RJ, Lee HS, Bakalchuk L, Tenenbaum C, Westfal RE. Improved outcomes in patients with acute allergic syndromes who are treated with combined H₁ and H₂ antagonists. *Ann Emerg Med* 2000; 36: 462–8.