

Catecholamine responses to histamine infusion in man

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To evaluate the effects of histamine-induced hypotension on plasma catecholamine levels, eight normal men, aged 20 to 40 years, were infused with incremental doses of histamine starting at 0.2 µg/kg/min at a 30 degree tilt position with monitoring of blood pressure (BP) and heart rate. Histamine dosage was increased every 5 minutes by 0.1 to 0.2 µg/kg/min until mean BP fell >15 mm Hg or a dosage of 1.6 µg/kg/min was reached. Plasma catecholamine samples were taken between the fourth and fifth minute of each histamine dosage. Identical measurements were made during nitroglycerin-induced hypotension in these subjects. Histamine produced threefold greater increases in heart rate and plasma norepinephrine (NE) levels than did nitroglycerin for comparable decreases in BP. Although NE levels increased twofold to fivefold from baseline with histamine infusion, epinephrine levels increased minimally at the highest doses or not at all. Our data demonstrate that histamine selectively releases NE from adrenergic nerve terminals without significant adrenal catecholamine release. We suggest that neural NE release plays an important role in the cardiac effects of histamine. (J ALLERGY CLIN IMMUNOL 1991;87:499-504.)

The importance of catecholamines in anaphylactic shock has been emphasized by the increased severity and resistance to treatment of anaphylaxis in subjects receiving β -adrenergic antagonists.¹⁻¹⁰ The severity and difficulty in clinical management has been due primarily to cardiovascular manifestations, including profound systemic hypotension, bradycardia, and myocardial depression. Although most reported cases have been in individuals receiving the β_1 - and β_2 -antagonist, propranolol, other cases have been reported with selective β_1 -antagonists.^{5, 7} This finding suggests that a major factor in such cases may be the blockade of compensatory cardiac β_1 -responses, both chronotropic and inotropic.

Histamine, a major mediator of human anaphylaxis, has been demonstrated to have positive inotropic and

Abbreviations used

NE: Norepinephrine
NTG: Nitroglycerin
BP: Blood pressure
HR: Heart rate

chronotropic cardiac effects in humans¹¹⁻¹³ and in isolated human heart tissue.^{14, 15} Although the functional contributions of histamine-receptor subtypes have been evaluated in vitro and in vivo,¹¹⁻¹⁵ studies to date have not characterized whether these histamine effects on the intact human heart may be mediated via reflex or direct activation of sympathetic nerves with the release of NE stimulating innervated cardiac β_1 -receptors. It is widely accepted that histamine directly releases catecholamines from the adrenals based on early animal studies and inferential observations in some patients with pheochromocytoma. The cardiac effects of histamine in the isolated hearts of cats and rats are, indeed, totally explained by direct release of NE.¹⁶

The present study was undertaken, first, to determine whether histamine selectively released individual catecholamines (NE versus epinephrine) as indicators of organ-specific effects, and, second, to determine if the tachycardia produced by histamine was greater than tachycardia caused by baroreceptor stimulation as a response to the hypotension produced. To evaluate this second goal, we chose to compare the

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effects of comparable degrees of hypotension induced by NTG with effects of histamine on heart rate and plasma catecholamine levels.

METHODS

Subjects

Eight normal men, aged 20 to 40 years, with no previous history of asthma, anaphylaxis, or cardiac or ulcer disease, were included in the study protocol that was approved by the Ethics Committees of St. Paul's Hospital and the University of British Columbia. Informed consent was obtained from each subject. Subjects were studied in the morning and refrained from ingestion of caffeine. No subject was taking medication of any type.

Study protocol

Histamine phosphate (Allen and Hanburys, Vancouver, British Columbia) and NTG (Roussel Canada, Inc., Montreal, Quebec) infusions were done on separate occasions. Subjects were maintained head uppermost on a 30 degree tilt table. A No. 18 intravenous catheter was placed into the left antecubital vein to which was connected a three-way stopcock with a syringe containing heparinized saline on one port and the sampling syringe on the other port. Drug was infused through a No. 20 intravenous catheter placed in the right antecubital vein. Drug infusions were performed with a Harvard (Harvard Apparatus, South Natick, Mass.) infusion pump. An automatic vital signs monitor (Dinamap, Critikon, Inc., Tampa, Fla.) recorded systolic, diastolic, mean BPs, and HR at 1-minute intervals. A 30-minute baseline period before drug infusion was used, ensuring that mean BP and HR had stabilized for 15 minutes (individual values not varying >5% for mean BP and 10% for HR).

Histamine infusion was commenced at 0.2 $\mu\text{g/kg/min}$ and increased at 5-minute intervals by 0.1 or 0.2 $\mu\text{g/kg/min}$. The infusion was stopped when the BP fell by >15 mm Hg or a dosage of 1.6 $\mu\text{g/kg/min}$ was reached. NTG infusions were performed in an analogous manner beginning at 0.2 $\mu\text{g/kg/min}$ with incremental dose increases every 5 minutes until a fall in mean BP of >15 mm Hg. All drugs were diluted to the desired concentration with normal saline.

Blood samples collected in heparinized tubes were obtained during the baseline state and between the fourth and fifth minute of infusion of each drug dosage. Samples were stored on ice and centrifuged at 4°C. Plasma was stored at -75°C until assay.

Measurements of catecholamines

Plasma NE and epinephrine levels were quantitated in subject batches with electrochemical detection (Metrohm detector, Brinkmann Instruments, Inc., Rexdale, Ontario) of individual catecholamines eluted from a Hypersil ODS 5 μm reverse-phase column with high-performance liquid chromatography.^{17, 18} Detection limit was 13 pg/ml for epinephrine with basal values being ≤ 13 pg/ml in four of 16 samples. The detection limit was the same for NE with basal values all being >100 pg/ml. The individual performing these assays was unaware of the drug

treatment or physiologic response to the infusion administered.

Data processing and statistical analysis

For each drug dosage, the mean value of BP and HR taken during the last 4 minutes of each 5-minute infusion period was used for data analysis. Correlation of these indices with plasma catecholamine values (means of duplicate determinations) was performed with Pearson's regression analysis.

RESULTS

All subjects were normotensive with baseline means BP ranging from 69.6 to 93.0 mm Hg and resting HRs from 55 to 82 beats/min. All subjects had normal baseline catecholamine levels for 30 degree tilt with a range of NE from 233 to 455 pg/ml and a range of epinephrine from <13 (four of 16 samples) to 52 pg/ml. The intra-assay coefficient of variation for NE determinants was 2.2% for values approximating 1000 pg/ml and a 4.5% for values approximating 100 pg/ml. The coefficient of variation for epinephrine determinations was 6.4% for values approximating 100 pg/ml, 19.0% for those approximating 40 pg/ml, and 38.7% for those approximating 20 pg/ml. Interassay coefficients of variation were comparable to intra-assay coefficients of variation.

Two individual subject responses demonstrating the responses to histamine and NTG are illustrated in Fig. 1. No subject demonstrated a decrease of >5 mm Hg with the starting dosage. The doses causing a drop in mean BP of 5, 10, 15, and 20 mm Hg are presented in Table I.

As anticipated, HRs increased as BP fell for both drugs but, for comparable drops in BP, HRs rose more with histamine than with NTG (Fig. 1). Changes in HR were closely correlated with changes in BP for both NTG and histamine infusion (Table II). For comparable changes in BP, plasma NE changes were significantly greater for histamine infusion than for NTG infusion (Fig. 2). The slopes of regression lines (-35.68 for histamine and -10.71 for NTG) revealed a threefold greater NE response for histamine than for NTG ($p < 0.05$).

Changes in HR versus plasma NE for each dose of drug in all subjects are illustrated in Fig. 3. Note that both HR and NE values were greater with histamine infusion than with NTG and that these two parameters were better correlated for histamine than for NTG (correlation coefficients of 0.627 for histamine versus 0.421 for NTG, Table II). The slopes of the regression lines (19.51 for histamine and 5.91 for NTG) revealed a threefold greater response with histamine ($p < 0.05$).

Plasma epinephrine levels demonstrated minimal increases with infusion of either histamine or NTG in all subjects. The differential responses in plasma NE

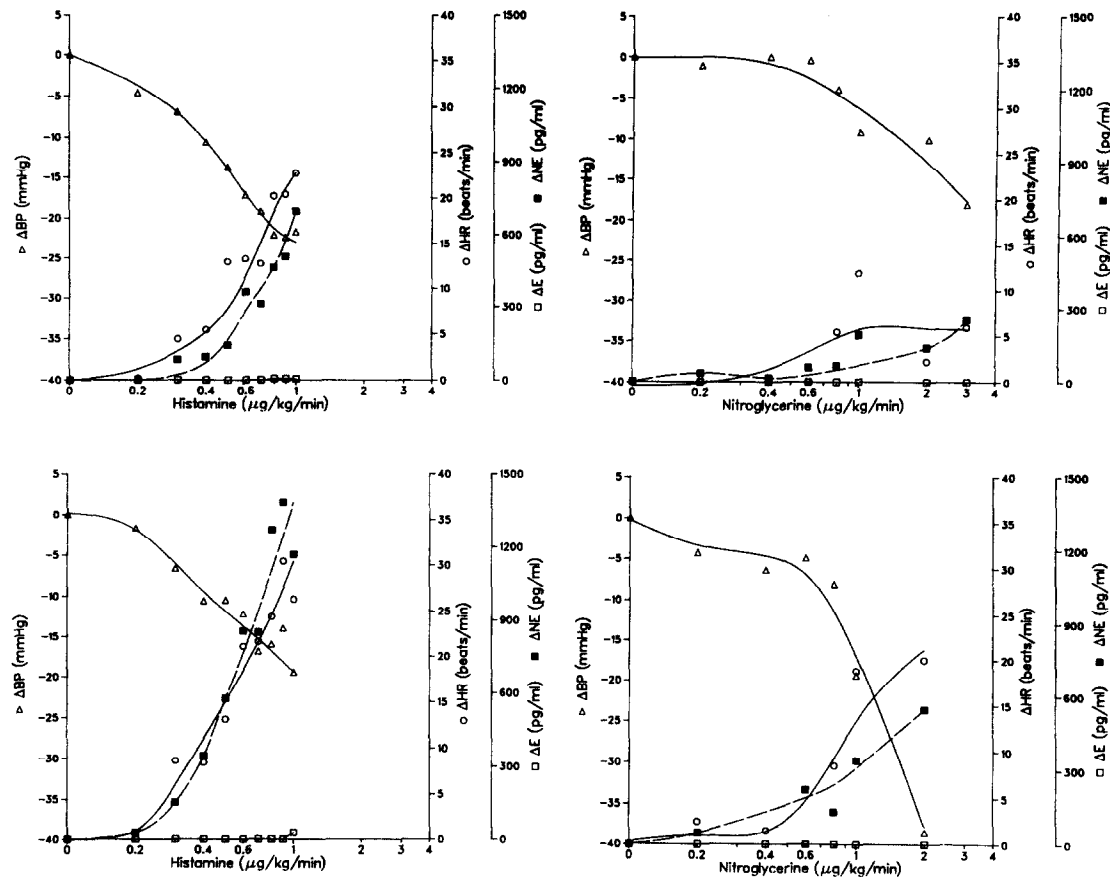


FIG. 1. Hemodynamic and catecholamine responses to histamine and NTG infusions for two subjects. Changes in mean BP (Δ BP, Δ — Δ), HR (Δ HR, $\circ$ — $\circ$), plasma NE (Δ NE, $\blacksquare$ — $\blacksquare$), and epinephrine (Δ E, $\square$ — $\square$) are plotted for each histamine and NTG dose.

TABLE I. Reactivity to infused drug

Subject No.	Histamine				NTG			
	PD ₅	PD ₁₀	PD ₁₅	PD ₂₀	PD ₅	PD ₁₀	PD ₁₅	PD ₂₀
1	0.55	0.59	0.78	—	0.47	0.95	3.38	—
2	0.34	0.58	0.97	>1.6	0.22	0.85	0.91	1.0
3	0.25	0.38	0.71	1.0	1.50	2.35	3.06	3.28
4	0.36	0.47	0.63	0.86	0.69	0.90	1.22	1.68
5	0.20	0.38	0.53	0.71	0.84	1.0	2.52	—
6	0.43	0.70	>1.6	—	1.10	2.22	2.61	2.75
7	0.42	0.81	0.93	>1.6	0.55	0.73	0.85	0.96
8	0.76	1.52	>1.6	—	0.28	1.15	1.84	—

PD, Provocative dose (micrograms per kilogram per minute) producing a decrease in mean BP of 5 mm Hg (PD₅), 10 mm Hg (PD₁₀), 15 mm Hg (PD₁₅), and 20 mm Hg (PD₂₀).
Values are derived by interpolation from the original drug dose-response curves connecting individual data points.

and epinephrine can be observed for individual subjects in Fig. 1 and Table III.

In all subjects, the flushing and hypotension with histamine was very transient, with BP and HR returning to baseline values within 2 minutes. Plasma NE levels measured 30 minutes after the infusion of either histamine or NTG had returned to baseline values.

DISCUSSION

Previous studies have evaluated the hemodynamic effects of histamine infusion in man.^{11-13, 19-22} Our protocol differed from these studies in two aspects. One difference was the maintenance of subjects at 30 degree tilt that produced more pronounced changes in BP with histamine infusion because of pooling in the splanchnic bed and limbs,²³ increased baroreceptor-

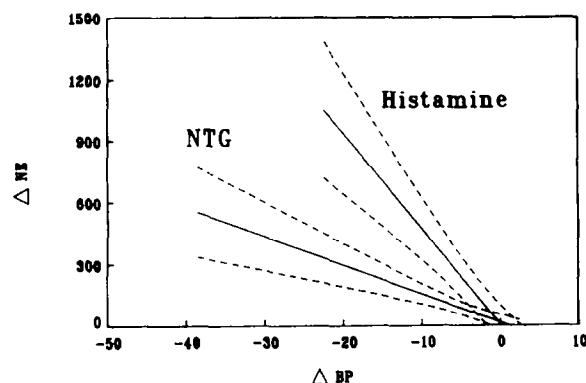


FIG. 2. Increases in NE (Δ NE) in picomoles per milliliter compared with decreases in mean BP (Δ BP) in millimeters of mercury for all doses of histamine ($n = 65$) and NTG ($n = 52$) in the eight subjects; 95% confidence intervals (*dashed lines*) for each regression line (*solid lines*) are illustrated.

mediated changes, and provided additional safety. Another difference was the use of multiple incremental doses of drug that provided dose responses for BP, HR, and plasma NE. These differences were reproducible when they were evaluated on multiple occasions in two subjects, suggesting the technique would be more reliable than previous methods for assessment of pharmacologic intervention. Because of the short duration of action of histamine with return of BP and HR to baseline values within 10 minutes and plasma NE within 30 minutes (not evaluated at earlier times) of stopping infusion, it should also be possible to assess the effects of certain pharmacologic agents by repeating the histamine infusion during the same study session.

Analysis of the increases in NE versus epinephrine during histamine infusion suggests that the adrenal gland is not the source of NE for the doses of histamine used. Small increases in epinephrine were observed in some subjects at the highest doses, suggesting the effect of histamine on adrenal catecholamine release requires much higher concentrations than concentrations for NE release from adrenergic nerves. The relative increase in NE versus epinephrine was much greater than was found for exercise.¹⁸ One other study has suggested histamine selectively increases NE,²² although the changes in NE levels were much less (<100 pg/ml) than we found, compatible with less histamine infused and lesser increase in HR. These results differ from results found by other investigators in various animal species¹⁶ in which there is good evidence for histamine release of catecholamines from adrenal glands. Two major differences between our study and these studies are readily apparent. Humans are remarkably more sensitive to the cardiovascular

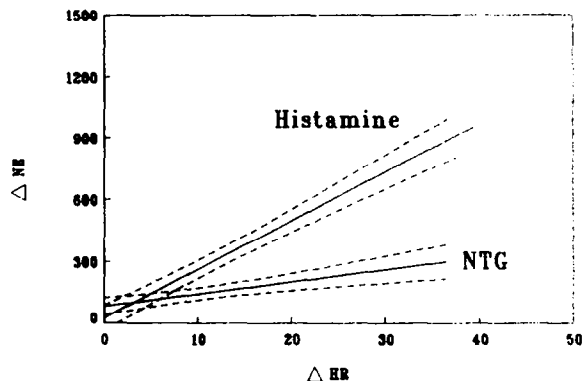


FIG. 3. Increases in NE (Δ NE) in picograms per milliliter compared with increases in HR (Δ HR) in beats per minute for all doses of histamine ($n = 65$) and NTG ($n = 52$) in the eight subjects; 95% confidence intervals (*dashed lines*) for each regression line (*solid lines*) are illustrated.

effects of histamine than many animal species. With a comparable protocol in small pigs, we have recently found that doses 200 times doses used in humans were required for comparable hemodynamic changes (Tsang J, Ohgami M, Schellenberg RR. Unpublished observation.). In a number of subjects we did get increases in plasma epinephrine, although increases were minimal, at the highest histamine doses. These subjects had comparable increases with NTG, suggesting the changes may be secondary to the hypotension. A second factor that may account for some of the differences noted is that most of the earlier animal experimentation was done before the development of highly sensitive and specific assays for plasma catecholamines.

Our findings suggest histamine releases NE by activating cardiac sympathetic nerves. That this may be partially through a direct action is suggested by our data demonstrating only one third the changes in heart rate and NE levels when NTG was used to produce comparable changes in BP. Since NE in the circulation has minimal activity relative to its actions when it is released in tissues, release from noncardiac sites (which is suggested by the differences in Δ NE/ Δ HR correlations for histamine and NTG) could not have produced the changes in HR. Studies with β -adrenergic blocking agents are required to address this question directly. It will be of interest to determine if β -antagonists inhibit the changes in both chronotropic and inotropic function caused by histamine infusion in man.¹¹⁻¹³ Although our study used no measurement of inotropy, all subjects reported the sensation that their hearts were beating more forcefully with histamine infusion. This sensation was not noted for NTG infusion.

TABLE II. Matrix of Pearson's correlation coefficients

	Histamine (n = 65)		NTG (n = 52)	
	BP	HR	BP	HR
HR	-0.654		-0.622	
NE	-0.602	0.627	-0.718	0.421

BP, Mean (millimeters of mercury); HR, beats per minute; NE, picograms per milliliter of plasma.

TABLE III. Plasma catecholamine responses to infused drug

Subject No.	Histamine			NTG		
	Δ BP _{max}	Δ NE _{max}	Δ E _{max}	Δ BP _{max}	Δ NE _{max}	Δ E _{max}
1	18.2	1196	0	19.0	514	0
2	14.6	1033	20	38.5	547	0
3	19.5	1383	29	32.6	513	0
4	20.0	300	0	33.8	129	0
5	22.4	696	0	18.1	254	0
6	12.4	452	55	23.2	128	28
7	16.9	646	102	34.9	353	62
8	12.5	771	117	15.9	313	108

E, Epinephrine, picograms per milliliter; BP, mean (millimeters of mercury); NE, picograms per milliliter of plasma. All values are expressed as the maximal difference (Δ_{max}) from the baseline preinfusion period.

Recently, increasing evidence has demonstrated that the severity of anaphylaxis is increased in individuals taking β-adrenergic antagonists.¹⁻¹⁰ This may be due to a number of different mechanisms or more likely a combination of more than one mechanism. β-Adrenergic blockade may enhance release of mediators, including histamine from mast cells and basophils. Although β-adrenergic antagonists inhibit the effect of β-adrenergic agonists on mediator release,²⁴⁻²⁷ it is questionable whether β-antagonists actually enhance antigen-induced mediator release. If this were the primary mechanism, it would be expected not only to increase severity of anaphylaxis but to increase incidence of anaphylaxis in subjects receiving β-blockers. Although this may be the case, confirmatory data demonstrating an increased incidence is lacking.

Even if β-blockers do not accentuate histamine release in vivo, they would prevent therapeutic β-adrenergic agonists from inhibiting histamine release, a property well documented in numerous in vitro human preparations.²⁴⁻²⁸ If histamine release is ongoing,

this mechanism would decrease the therapeutic effect of epinephrine in individuals receiving β-blockers.

The increased severity of anaphylaxis in individuals receiving β-blockers suggests blockade of compensatory physiologic responses to systemic hypotension. It is obvious that one such factor inhibited by β-blockade would be the baroreceptor-mediated cardiac response. Our study suggests that in addition to this response to hypotension (demonstrated by the increase in HR and NE levels after NTG), histamine exerts cardiac effects via direct adrenergic nerve stimulation. Therefore, β-adrenergic blockade would inhibit the positive chronotropic and inotropic effects of histamine, leading to accentuated systemic hypotension and decreased perfusion.

In summary, our study suggests that histamine-induced tachycardia is mediated at least partially by direct activation of cardiac adrenergic nerves with the release of NE. These results suggest that blocking cardiac β₁-receptors would significantly inhibit the cardiac responses to histamine, which are compensatory for the systemic hypotension produced. Thus,

we would predict increased severity and worsened outcome of individuals receiving β -adrenergic blocking agents undergoing anaphylaxis, consistent with clinical observations.

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REFERENCES

- Jacobs RL, Rake GW, Fournier DC, Chilton RJ, Culver WG, Beckmann CH. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. *J ALLERGY CLIN IMMUNOL* 1981;68:125.
- Newman BR, Schultz LK. Epinephrine-resistant anaphylaxis in a patient taking propranolol hydrochloride. *Ann Allergy* 1981;47:35.
- Hannaway PJ, Hopper GDK. Severe anaphylaxis and drug-induced beta-blockade. *N Engl J Med* 1983;308:1536.
- Hamilton G. Severe adverse reactions to urography in patients taking β -adrenergic blocking agents. *Can Med Assoc J* 1985;133:122.
- Young C, Toogood JH. Do beta-blockers increase the risk of immunotherapy [Abstract]? *J ALLERGY CLIN IMMUNOL* 1986;77:225.
- Stark BJ, Sullivan TJ. Biphasic and protracted anaphylaxis. *J ALLERGY CLIN IMMUNOL* 1986;78:76.
- Zaloga GP, Delacey W, Holmboe E, Chernow B. Glucagon reversal of hypotension in a case of anaphylactoid shock. *Ann Int Med* 1986;105:65.
- Toogood JH. Beta-blocker therapy and the risk of anaphylaxis. *Can Med Assoc J* 1987;136:929.
- Lockey RF, Benedict LM, Turkeltaub PC, Bukantz SC. Fatalities from immunotherapy (IT) and skin testing (ST). *J ALLERGY CLIN IMMUNOL* 1987;79:660.
- Toogood JH. Risk of anaphylaxis in patients receiving beta-blocker drugs [Editorial]. *J ALLERGY CLIN IMMUNOL* 1988;81:1.
- Weiss S, Ellis LB, Robb GP. Bodily responses in man during continuous intravenous administration of histamine. *Am J Physiol* 1929;90:551.
- Vigorito C, Russo P, Picotti GB, Chiariello M, Poto S, Marone G. Cardiovascular effects of histamine infusion in man. *J Cardiovasc Pharmacol* 1983;5:531.
- Marone G, Triggiani M, Cirillo R, et al. Chemical mediators and the human heart. *Prog Biochem Pharmacol* 1985;20:38.
- Ginsburg R, Bristow MR, Stinson EB, Harrison DC. Histamine receptors in the human heart. *Life Sci* 1980;26:2245.
- Graver LM, Robertson DA, Levi R, Becker CG, Weksler BB, Gay WA. IgE-mediated hypersensitivity in human heart tissue: histamine release and functional changes. *J ALLERGY CLIN IMMUNOL* 1986;77:709.
- McNeill JH. Histamine and the heart. *Can J Physiol Pharmacol* 1984;62:720.
- Hjemdahl P, Daleskog M, Kahan T. Determination of plasma catecholamines by high-performance liquid chromatography with electrochemical detection: comparison with a radioenzymatic method. *Life Sci* 1979;25:131.
- Foster NK, Martyn JB, Rangno RE, Hogg JC, Pardy RL. Leukocytosis of exercise: role of cardiac output and catecholamines. *J Appl Physiol* 1986;61:2218.
- Kaliner M, Shelhamer JH, Ottesen EA. Effects of infused histamine: correlation of plasma histamine levels and symptoms. *J ALLERGY CLIN IMMUNOL* 1982;69:283.
- Duner H, Pernow B. Histamine in man under physiological and pathological conditions. *Acta Scand* 1960;168:307.
- 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.
- Watkins J, Dargie HJ, Brown MJ, Krikler DM, Dollery CT. Effects of histamine type 2 receptor stimulation on myocardial function in normal subjects. *Br Heart J* 1982;47:539.
- Dale HH, Laidlaw PP. The physiological action of β -iminazoly-ethylamine. *J Physiol* 1910;41:318.
- Assem ESK, Schild HO. Inhibition by sympathomimetic amines of histamine release induced by antigen in passively sensitized human lung. *Nature* 1969;224:1028.
- Assem ESK, Schild HO. Antagonism by β -adrenoceptor blocking agents of the antianaphylactic effect of isoprenaline. *Br J Pharmacol* 1971;42:620.
- Lichtenstein LM, DeBernardo R. The immediate allergic response: in vitro action of cyclic AMP-active and other drugs on the two stages of histamine release. *J Immunol* 1971;107:1131.
- Butchers PR, Skidmore IF, Vardey CJ, Wheeldon A. Characterization of the receptor mediating the anti-anaphylactic effects of β -adrenoceptor agonists in human lung tissue in vitro. *Br J Pharmacol* 1980;71:663.
- Lichtenstein LM, Margolis S. Histamine release in vitro: inhibition by catecholamines and methylxanthines. *Science* 1968;161:902.