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ORIGINAL ARTICLE

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Histaprodifen, methylhistaprodifen, and dimethylhistaprodifen are potent H_1-receptor agonists in the pithed and in the anaesthetized rat

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Abstract Selective H_2- and H_3-receptor agonists, exhibiting an at least tenfold higher potency than histamine itself at the respective receptors, have been known for several years. Selective H_1-receptor agonists with a potency exceeding that of histamine have become available only recently; the most potent are methylhistaprodifen and dimethylhistaprodifen [N^{α}-methyl- and N^{α},N^{α}-dimethyl-2-(3,3-diphenylpropyl)histamine, respectively] with 3.4- and 2.4-fold higher potencies than histamine in vitro (in the guinea-pig ileum). The aim of the present study was to examine whether these compounds and the parent compound histaprodifen are potent H_1-receptor agonists in the pithed and in the anaesthetized rat.
In pithed, vagotomized rats diastolic blood pressure was decreased by 2-(2-thiazolyl)ethanamine i.v. (which was used as a reference H_1-receptor agonist) and by histaprodifen, methylhistaprodifen, and dimethylhistaprodifen; the maximum decrease was about 45 mmHg for each compound, and the potencies, expressed as pED_{50}, the negative logarithm of the dose (in mole per kilogram body weight) eliciting a half-maximal response, were 7.23, 7.55, 8.43 and 8.12, respectively. The dose/response curves of the four compounds were shifted to the right to about the same extent by the H_1-receptor antagonist dimetindene (1 µmol/kg i.v.). The vasodepressor response was not affected by combined i.v. administration of the H_2- and H_3-receptor antagonists ranitidine and thioperamide, by combined i.v. administration of the α_1- and α_2-adrenoceptor antagonists prazosin and rauwolscine, and by the β-adrenoceptor antagonist propranolol i.v. but was attenuated by the inhibitor of NO synthase, N^{ω}-nitro-L-arginine methyl ester i.v. In anaesthetized rats 2-(2-thiazolyl)ethanamine, histaprodifen, methylhistaprodifen and dimethylhistaprodifen i.v. also decreased diastolic blood pressure in a manner sensitive to dimetindene i.v.
Our data show that histaprodifen and, in particular, methyl- and dimethylhistaprodifen are highly potent H_1-receptor agonists in vivo.

Key words Histaprodifen · Methylhistaprodifen · Dimethylhistaprodifen · 2-(2-Thiazolyl)ethanamine · H_1-receptor agonists · Pithed rats · Anaesthetized rats · Dimetindene

Introduction

Histamine acts via three types of receptors, termed H_1, H_2 and H_3 (for review, see Arrang 1994; Leurs et al. 1995; Hill et al. 1997). For each receptor subtype, potent antagonists are available (for review, see Hill et al. 1997). H_2- (Buschauer and Baumann 1991; van der Goot et al. 1991) and H_3-receptor agonists (Lipp et al. 1992a,b; Vollinga et al. 1994) with a potency exceeding that of histamine by a factor of 10 or more have also been synthesized. On the other hand, it has proven difficult to synthesize H_1-receptor agonists with a potency equalling or exceeding that of histamine. Relatively potent H_1-receptor agonists were found in a series of meta-substituted 2-phenylhistamines (Koper et al. 1990; Zingel et al. 1990, 1995; Leschke et al. 1995); one compound of this series, 2-(3-(trifluoromethyl)phenyl)histamine, was more potent than histamine, with a relative potency of 128 (potency of histamine set at 100) in the guinea-pig ileum (Leschke et al. 1995). Very recently, derivatives of histamine, substituted at C-2 of the imidazole ring with a 3,3-diphenylpropyl moiety and at the N^{α} atom with one (methylhistaprodifen; relative potency 343) or two (dimethylhistaprodifen; relative potency 242) methyl

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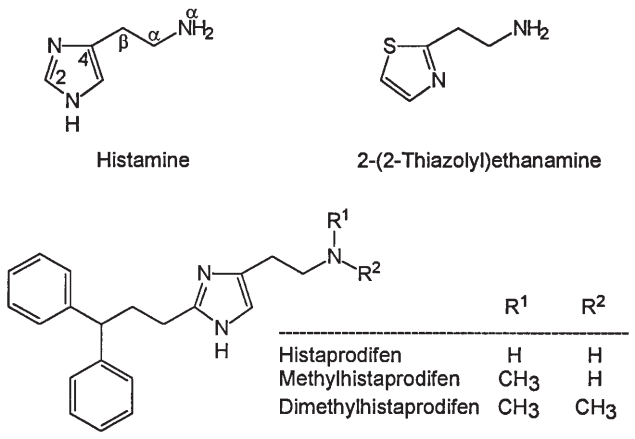


Fig. 1 Structures of histamine and the four H_1-receptor agonists examined in the present study

groups have proven to be even more potent H_1 receptor agonists (Elz et al. 1998; for chemical structures, see Fig. 1).

Thus far, the latter two compounds and their analogue histaprodifen (lacking a methyl group on the N^{α} atom; relative potency of 111) have been studied in vitro only (Elz et al. 1998). The aim of this paper was to study whether the potent agonism of these three compounds at the H_1 receptor can also be shown in the pithed and in the anaesthetized rat. For this purpose, the effect of these compounds and of 2-(2-thiazolyl)ethanamine (which served as a reference H_1-receptor agonist) on diastolic blood pressure was determined and the interaction of these H_1-receptor agonists with the H_1-receptor antagonist dimetindene was studied. In addition, we examined in pithed rats whether the effect of the four H_1-receptor agonists is affected by inhibition of NO synthase by N^{ω}-nitro-L-arginine methyl ester (L-NAME) and whether endogenous catecholamines contribute to the overall effect of the H_1-receptor agonists.

Materials and methods

Pithed rat. Male Wistar rats weighing 180–300 g were anaesthetized with pentobarbitone sodium 300 µmol/kg i.p. and then injected with atropine 2 µmol/kg i.p. After cannulation of the trachea the animals were pithed and artificially ventilated with air (60 strokes/min) using a respiratory system (Medipan, Warsaw, Poland). Both vagal nerves were cut. Diastolic blood pressure was measured from the right carotid artery via a pressure transducer (Gould P 23 ID); the pressure wave triggered a rate-meter. Body temperature was kept constant at approximately 36 °C using a tungsten lamp and monitored by a rectal probe transducer. The transducers were connected to the monitor Trendscope 8031 (Artema, Białystok, Poland). The left femoral vein was cannulated for i.v. administration of drugs in a volume of 0.5 ml/kg. Following pithing, diastolic blood pressure was routinely raised to about 85 mmHg by infusion of vasopressin (0.04–0.4 IU/kg/min) into the right femoral vein (since vasopressor/vasodepressor effects are more marked at a higher level of blood pressure; see e.g. Malinowska and Schlicker 1993a).

After 15–30 min equilibration, during which the cardiovascular parameters were allowed to stabilize, propranolol 3 µmol/kg was injected i.v. to block the indirect sympathomimetic action of the highest dose of 2-(2-thiazolyl)ethanamine (the reference compound). Propranolol 3 µmol/kg was also administered to rats which received other histamine H_1-receptor agonists to ensure identical experimental conditions.

Anaesthetized rat. Rats were anaesthetized with urethane 14 mmol/kg i.p. The trachea was cannulated. Blood pressure, heart rate and temperature were measured as described above. In rats with a lower level of basal diastolic blood pressure, vasopressin was infused to raise diastolic blood pressure to about 85 mmHg. Experiments were begun after 15–30 min equilibration.

Experimental protocol. The effects of each of the four histamine H_1-receptor agonists (given i.v.) under control conditions and in the presence of the H_1-receptor antagonist dimetindene 1 µmol/kg i.v. on diastolic blood pressure and heart rate were studied in separate animals (only one dose/response curve per animal). Animals received increasing doses of the drug with sufficient time for full recovery to the pre-injection value. In some experiments the effects of two different H_1-receptor agonists (only one dose each), administered in various combinations and with alternating sequences, were examined. The first agonist (or the lowest dose of the agonist when a dose/response curve was to be constructed) was injected 5 min after administration of propranolol (only in pithed rats) given i.v. together with antagonists of various receptors or saline solution (control). L-NAME 37 µmol/kg was injected i.v. 10 min before propranolol (in this experimental group all experiments were performed in the absence of vasopressin since L-NAME itself raised diastolic blood pressure to about 85 mmHg).

Calculations and statistics. To assess the potency of the H_1-receptor agonists, we determined the negative logarithms of the doses decreasing blood pressure by 23 mmHg, i.e. by 50% of the maximum effect of about 45 mmHg (see Table 1; pED_{50}). Results are given as means±SEM throughout (*n* is the number of rats). For comparison of mean values the *t*-test for paired or unpaired data was used. When two or more treatment groups were compared with the same control group, Bonferroni's procedure was used. The differences were considered as significant when $P<0.05$.

Drugs used. The following drugs were used: histaprodifen dihydrogenmaleate, methylhistaprodifen dihydrogenmaleate, dimethylhistaprodifen dihydrogenoxalate (synthesized at the Institut für Pharmazie I, Freie Universität Berlin, Berlin, Germany), 2-(2-thiazolyl)ethanamine dihydrochloride (SKF, Brockham Park, UK), dimetindene maleate (Zyma, Munich, Germany), ranitidine hydrochloride (Glaxo, Ware, UK), thioperamide (free base; Professor J.C. Schwartz, Centre Paul Broca de l'INSERM, Paris, France), atropine sulphate, Lys^8-vasopressin, L-NAME, prazosin hydrochloride (Sigma, Deisenhofen, Germany), (-)-propranolol hydrochloride (ICI, Macclesfield, UK), rauwolscine hydrochloride (Roth, Karlsruhe, Germany), pentobarbitone sodium (Biowet, Puławy, Poland). Drugs were dissolved in water (atropine sulphate, pentobarbitone sodium) or saline with the following exceptions: histaprodifen dihydrogenmaleate and methylhistaprodifen dihydrogenmaleate were dissolved in a mixture of saline and ethanol 95% (20:1), dimethylhistaprodifen dihydrogenoxalate in a mixture of saline and dimethylsulphoxide (DMSO, 1:10), thioperamide (free base) in a mixture of saline and DMSO 9:1, and prazosin hydrochloride in a mixture of HCl 0.01 mol/l and DMSO 4:1. The vehicles for histaprodifen and its derivatives, thioperamide, and prazosin did not affect basal blood pressure and heart rate.

Results

Diastolic blood pressure

In all experimental groups diastolic blood pressure immediately prior to injection of the first dose of particular ligands

was about 85 mmHg (Table 2), either spontaneously or due to i.v. infusion of vasopressin (0.04–0.4 IU/kg/min) or administration of L-NAME (37 µmol/kg i.v.). In *pithed*, vagotomized rats, propranolol 3 µmol/kg i.v. caused a transient decrease in blood pressure within 1 min after administration, when given alone (8.8±0.9 mmHg; n=25; P<0.001) or together with the H_1-receptor antagonist dimetindene 1 µmol/kg (9.9±2.5 mmHg; n=15; P<0.01) or with the combination of the α_1-adrenoceptor antagonist prazosin 1 µmol/kg and the α_2-adrenoceptor antagonist rauwolscine 1 µmol/kg (18.1±1.5 mmHg; n=11; P<0.001). (When propranolol was given together with the H_2 antagonist ranitidine 1 µmol/kg plus the H_3 antagonist thioperamide 1 µmol/kg, no such decrease in blood pressure occurred).

In pithed, vagotomized rats, the histamine H_1 receptor agonists 2-(2-thiazolyl)ethanamine, histaprodifen, methylhistaprodifen and dimethylhistaprodifen i.v. dose-dependently decreased diastolic blood pressure (Figs. 2 and 3). In all cases the maximum effect was about 45 mmHg (Table 1). The rank order of potencies of the drugs based on their pED_{50} values was: methylhistaprodifen>dimethylhistaprodifen>histaprodifen>2-(2-thiazolyl)ethanamine (Table 1).

The time course of the hypotensive effects was as follows: The maximal vasodepressor response for each dose of the four agonists was reached within 15 s. In the case of 2-(2-thiazolyl)ethanamine the hypotensive effects lasted for less than 1 min and about 2 min (at doses of 1 or less and 10 µmol/kg, respectively) and in the case of histaprodifen or its derivatives for less than 2 min, about 5 min or about 10 min (at doses of 0.1 or less, 1 and 10 µmol/kg, respectively).

The H_1-receptor antagonist dimetindene 1 µmol/kg i.v. caused a marked rightward shift in the dose/response curves for all agonists (negative logarithm of (dose ratio–1) 1.55–1.86, SEMs 0.07–0.24; Figs. 2 and 3). As shown in Figs. 2 and 3 the maximal vasodepressor responses to all compounds were almost the same in the absence and in the presence of propranolol 3 µmol/kg. They were also not influenced by combined α_1- and α_2-adrenoceptor blockade

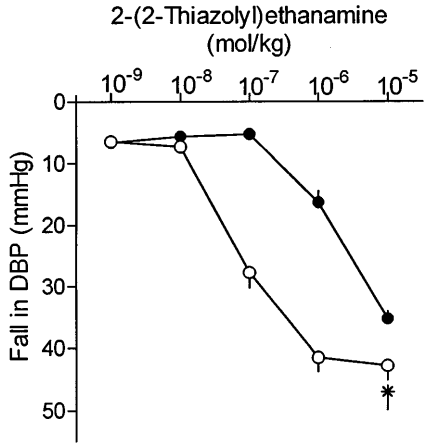
Table 1 Maximum effect (E_{max}) and potency (expressed as the negative logarithm of the agonist dose eliciting a half-maximal response, in this case a fall in diastolic blood pressure of 23 mmHg, pED_{50}) of the four H_1-receptor agonists examined in the present study [*2TEA* 2-(2-thiazolyl)ethanamine, *HAP* histaprodifen, *MHAP* methylhistaprodifen, *DMHAP* dimethylhistaprodifen] with respect to their vasodepressor effect in pithed, vagotomized rats. The values of E_{max} and pED_{50} were derived from the dose/response curves obtained for the H_1-receptor agonists in Figs. 2 and 3. E_{max} values are given as means±SEM of three to six rats; in the case of DMHAP the mean is based on two individual values given in *brackets*

H_1-receptor agonist	E_{max} (mmHg)	pED_{50}
2TEA	42.8 ± 2.3	7.23 ± 0.03
HAP	46.0 ± 2.0	7.55 ± 0.06
MHAP	45.8 ± 1.0	8.43 ± 0.04
DMHAP	46.5 (44.0, 49.0)	8.12 ± 0.10

Table 2 Influence of the histamine H_1-receptor agonists 2TEA, HAP, MHAP and DMHAP on diastolic blood pressure (DBP) in anaesthetized and in pithed rats under various experimental conditions. Drugs were administered i.v. (unless stated otherwise). Means±SEM of 4–23 rats (DBP prior to injection of H_1-receptor agonists) and of 3–7 rats (effects of H_1-receptor agonists)

Experimental groups		DBP (mmHg) before injection of H_1 agonist	Decrease in DBP (mmHg) induced by			
			2TEA 0.1 µmol/kg	HAP 0.1 µmol/kg	MHAP 0.01 µmol/kg	DMHAP 0.01 µmol/kg
Pithed, vagotomized rats, pre-treated with atropine 2 µmol/kg i.p., propranolol 3 µmol/kg i.v.	Control	86.2 ± 0.6	27.7 ± 2.5	35.8 ± 2.0	31.3 ± 1.3	25.6 ± 2.2
	Dimetindene 1 µmol/kg	85.7 ± 0.4	5.3 ± 0.9***	7.3 ± 1.3***	6.8 ± 0.5***	6.5 ± 0.9***
	Ranitidine 1 µmol/kg plus thioperamide 1 µmol/kg	85.5 ± 0.7	24.5 ± 3.1	37.0 ± 3.1	31.5 ± 4.1	26.3 ± 2.4
	L-NAME 37 µmol/kg	89.3 ± 3.5	14.5 ± 2.5**	22.5 ± 3.8*	20.8 ± 2.3*	12.6 ± 2.8**
Anaesthetized rats	Control	86.6 ± 1.5	25.3 ± 1.3	34.8 ± 3.1	30.4 ± 3.2	25.2 ± 4.0
	Dimetindene 1 µmol/kg	84.8 ± 2.2	14.0 ± 2.9**	18.0 ± 4.6*	16.5 ± 1.9**	13.0 ± 0.6*

* P<0.05, **P<0.01, ***P<0.001 vs. corresponding control



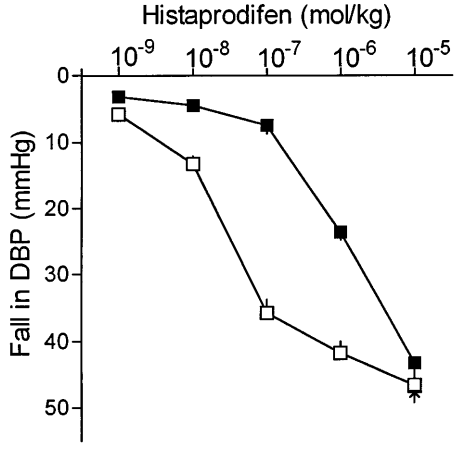
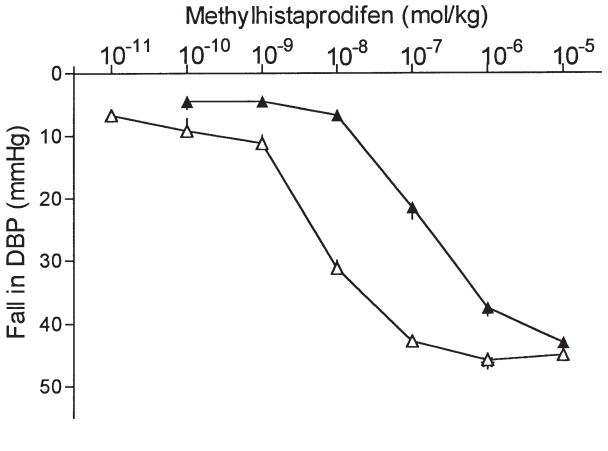


Fig. 2 Effects of 2-(2-thiazolyl)ethanamine and histaprodifen i.v. on diastolic blood pressure (*DBP*) in pithed, vagotomized rats. DBP was adjusted to a level of about 85 mmHg by i.v. infusion of vasopressin. Prior to injection of the H_1-receptor agonist under study, the rats received an i.v. injection of propranolol 3 µmol/kg (*open symbols*), propranolol plus dimetindene 1 µmol/*kg (solid symbols*) or saline (*). For further details, see text. Means±SEM of four to six rats. For some points, the SEM is smaller than the diameter of the *symbol*



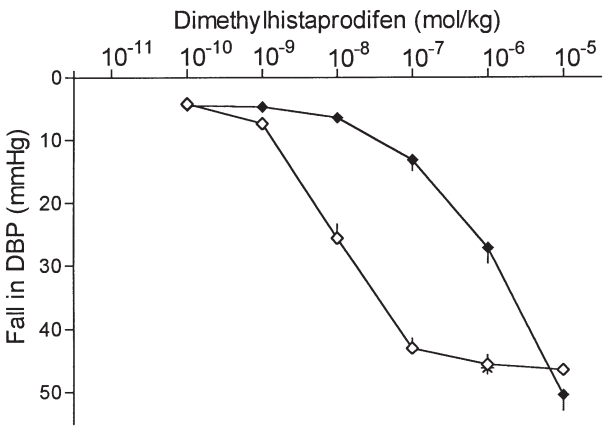


Fig. 3 Effects of methylhistaprodifen and dimethylhistaprodifen i.v. on DBP in pithed, vagotomized rats. DBP was adjusted to a level of about 85 mmHg by i.v. infusion of vasopressin. Prior to injection of the H_1-receptor agonist under study, the rats received an i.v. injection of propranolol 3 µmol/kg (*open symbols*), propranolol plus dimetindene 1 µmol/kg (*solid symbols*) or saline (*). For further details, see text. Means±SEM for three to six rats or of two rats (only dimethylhistaprodifen 10 µmol/kg with propranolol). For some points, SEM is smaller han the diameter of the *symbol*

(prazosin 1 µmol/kg given i.v. together with rauwolscine 1 µmol/kg; data not shown).

Table 2 shows the hypotensive effects of the four H_1 receptor agonists given at doses approximately equal to their ED_{50}. The vasodepressor responses to 2-(2-thiazolyl)ethanamine and histaprodifen at doses of 0.1 µmol/kg and methylhistaprodifen and dimethylhistaprodifen at doses of 0.01 µmol/kg were inhibited by about 75–80% by the H_1-receptor antagonist dimetindene 1 µmol/kg, but they were not changed by the H_2-receptor antagonist ranitidine 1 µmol/kg given i.v. together with the H_3-receptor antagonist thioperamide 1 µmol/kg. We also studied the influence of an inhibitor of the biosynthesis of nitric oxide by vascular endothelial cells. L-NAME 37 µmol/kg i.v. diminished the vasodepressor responses to 2-(2-thiazolyl)ethanamine, histaprodifen, methylhistaprodifen, and dimethylhistaprodifen by 35–50% (Table 2).

In *anaesthetized* rats all H_1-receptor agonists (administered i.v.) induced almost the same decrease in blood pressure as in pithed, vagotomized rats (Table 2). The hypotensive responses in anaesthetized rats were also sensitive to dimetindene 1 µmol/kg i.v. and in its presence they were inhibited by about 45–50%.

Heart rate

In *pithed*, vagotomized rats basal heart rate immediately before injection of the H_1-receptor ligands was 320–360 beats/min. Propranolol 3 µmol/kg given i.v. 5 min earlier alone or in combination with antagonists at different receptors caused a transient (lasting about 1–2 min) decrease in this parameter by about 5–10% (data not shown). L-NAME 37 µmol/kg i.v. failed to affect basal heart rate, which was

also not changed by the H_1-receptor agonists at doses up to 1 µmol/kg i.v. The highest doses of histaprodifen and its derivatives (10 µmol/kg) slightly decreased heart rate by about 10–30 beats/min both in the absence or presence of dimetindene 1 µmol/kg i.v. In the absence of propranolol, histaprodifen 10 µmol/kg, methylhistaprodifen and dimethylhistaprodifen, 1 µmol/kg each, failed to influence heart rate. However, 2-(2-thiazolyl)ethanamine 10 µmol/kg caused a significant increase in heart rate by 70.7±2.7 beats/min (n=5), which was completely abolished by propranolol 3 µmol/kg (data not shown).

In *anaesthetized* rats, basal heart rate (290–380 beats/min), was not affected by i.v. injection of 2-(2-thiazolyl)ethanamine 0.1 µmol/kg, histaprodifen 0.1 µmol/kg, methylhistaprodifen 0.01 µmol/kg, or dimethylhistaprodifen 0.01 µmol/kg, either in the absence or presence of dimetindene 1 µmol/kg i.v. (data not shown).

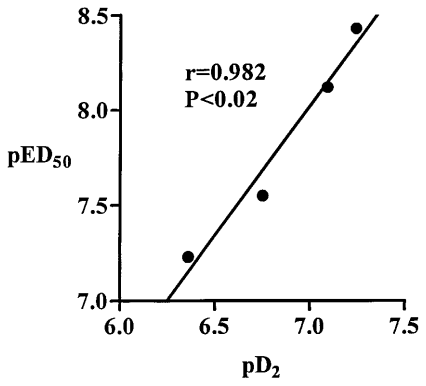


Fig. 4 Comparison of the potencies of the four H_1-receptor agonists in the pithed rat with their potencies at H_1 receptors in vitro. The potencies in the pithed rat (expressed as the negative logarithm of the dose eliciting a half-maximal response, pED_{50}) were taken from Table 1, and the in vitro potencies [expressed as the negative logarithm of (dose ratio–1), pD_2] for the contractile effects of the compounds on the guinea-pig ileum) were taken from Leschke et al. (1995) and Elz et al. (1998). pD_2 and pED_{50} values were compared with each other by linear regression analysis; r is the correlation coefficient and P the probability. The equation of the regression line is y=1.36x-1.5

Discussion

The present study was carried out to examine whether histaprodifen and its N^{α}-methyl and N^{α},N^{α}-dimethyl analogues are potent H_1-receptor agonists in the pithed, vagotomized rat and in the anaesthetized rat. To achieve comparable conditions in all animals, vasopressin was used to increase diastolic blood pressure to about 85 mmHg in the few anaesthetized rats with a lower level of blood pressure and in all pithed rats (with a diastolic blood pressure of about 45 mmHg). In one series of pithed rats NO synthase was blocked by L-NAME (which evokes a hypertensive response in the rat by removing the endogenous vasodilator tone built up by NO; Gardiner et al. 1990; Malinowska and Schlicker 1993a; Nilsson et al. 1997); L-NAME was used in these experiments at a dose which increases diastolic blood pressure to about 85 mmHg. Since histamine activates each of the three histamine receptor subtypes and, in pithed rats, each of them affects diastolic blood pressure (Malinowska and Schlicker 1991, 1993a), the selective H_1-receptor agonist 2-(2-thiazolyl)ethanamine rather than histamine itself was chosen as a reference drug.

The three novel compounds mimicked 2-(2-thiazolyl) ethanamine in that they elicited a hypotensive response in a manner sensitive to the H_1-receptor antagonist dimetindene, suggesting that they are H_1-receptor agonists as well. The hypotensive effect of each of the four agonists was virtually identical in the pithed and in the anaesthetized rats. These findings are compatible with the view that the hypotensive effects in the anaesthetized rat are not accompanied by activation of the baroreceptor reflex and that they are solely due to activation of H_1-receptors outside the CNS. The possibility that H_1-receptors within the CNS play a role had to be considered since activation of H_1-receptors in the CNS influences cardiovascular parameters (for review, see Schwartz et al. 1991) and since the newly synthesized drugs, due to their lipophilic properties, may pass the blood-brain barrier (most likely dimethylhistaprodifen).

A more detailed analysis of the hypotensive effects of the four H_1-receptor agonists was performed in pithed rats. We found that the rightward shift of the dose/response curves by dimetindene was virtually identical for each of the four agonists. The agonists exhibited a similar maximum effect, but markedly varying potencies. The rank order of potencies was the same as that obtained for the four compounds in the guinea-pig ileum assay in vitro (Leschke et al. 1995; Elz et al. 1998). When comparing the potencies in the pithed rat and in the in vitro model by linear regression analysis, a highly significant correlation was obtained (Fig. 4).

The view that the three novel compounds act via H_1 and not via H_2 and/or H_3 receptors is confirmed by two further observations. First, the hypotensive effect of the novel compounds was not affected by the combined administration of the H_2-receptor antagonist ranitidine and the H_3-receptor antagonist thioperamide, given at doses high enough to cause a marked attenuation of H_2- and H_3-receptor-mediated effects in the pithed rat (Malinowska and Schlicker 1991, 1993a). Second, the hypotensive effects of the novel compounds were diminished in those experiments in which NO synthase was blocked by L-NAME. It is well-known that the hypotensive effect mediated via H_1 receptors involves the release of NO from the endothelium, whereas the H_2-receptor-mediated vasodepressor response is due to the activation of receptors located directly on the vascular smooth muscle (for review, see Hill et al. 1997).

Finally, the possibility had to be considered that the cardiovascular effects of the novel compounds are distorted by the simultaneous release of catecholamines (for review, see Hill et al. 1997). One would expect that catecholamines contribute to the overall effect of H_1-receptor agonists since activation of H_1 receptors causes catecholamine release

from the adrenal medulla. For example, in the pithed rat the hypotensive effect of the non-selective histamine receptor agonist N^{α}-methylhistamine is accompanied by an H_1-receptor-mediated hypertensive effect related to the release of catecholamines (acting via α-adrenoceptors); N^{α}-methylhistamine also increases heart rate due to the H_1-receptor-mediated release of catecholamines (acting via β-adrenoceptors) (Malinowska and Schlicker 1993b). In addition, for 2-(2-thiazolyl)ethanamine, the reference compound in the present study, an H_1-receptor-*independent* release of catecholamines (causing an increase in heart rate) was found; thus, the drug is a substrate of the neuronal noradrenaline transporter (Boudreau and Vohra 1991), and high doses evoke a desipramine-dependent, carrier-mediated release of catecholamines from the postganglionic sympathetic neurones (Boudreau and Vohra 1991; Malinowska et al. 1992; Malinowska and Schlicker 1993a). (This "side effect" of 2-(2-thiazolyl)ethanamine led us to use the β-adrenoceptor antagonist propranolol in almost all experiments in the pithed rat.)

In the present study, catecholamines did not contribute to the overall effects of the novel H_1-receptor agonists. Thus, combined blockade of α_1- and α_2-adrenoceptors did not increase the H_1-receptor-mediated hypotensive effect. Moreover, omission of propranolol did not reveal an increase in heart rate. The reason why H_1-receptor-mediated catecholamine release contributes to the cardiovascular effects of N^{α}-methylhistamine but not to those of the three novel compounds remains to be established.

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References

Arrang JM (1994) Pharmacological properties of histamine receptor subtypes. Cell Mol Biol 40:275–281

Boudreau NJ, Vohra MM (1991) The mechanism of [^{3}H]noradrenaline release by histamine and its analogs from the rat vas deferens. Can J Physiol Pharmacol 69:469–474

Buschauer A, Baumann G (1991) Structure-activity relationship of histamine H_2-agonists, a new class of positive inotropic drugs. Agents Actions [Suppl]33:231–256

Elz S, Kramer K, Pertz H, Schunack W (1998) Methylhistaprodifen and congeners: highly potent and selective histamine H_1 receptor agonists (abstract). Naunyn-Schmiedeberg's Arch Pharmacol 358 [Suppl 2]:R762

Gardiner SM, Compton AM, Kemp PA, Bennett T (1990) Regional and cardiac haemodynamic effects of N^{G}-nitro-L-arginine methyl ester in conscious, Long Evans rats. Br J Pharmacol 101:625–631

Goot H van der, Bast A, Timmerman H (1991) Structural requirements for histamine H_2 agonists and H_2 antagonists. In: Uvnäs B (ed) Histamine and histamine antagonists (Handbook of experimental pharmacology series, vol. 97). Springer, Berlin Heidelberg New York, pp 573–748

Hill SJ, Ganellin CR, Timmerman H, Schwartz JC, Shankley NP, Young JM, Schunack W, Levi R, Haas HL (1997) International Union of Pharmacology. XIII. Classification of histamine receptors. Pharmacol Rev 49:253–278

Koper JG, Vliet A van der, Goot H van der, Timmerman H (1990) New selective H_1 agonists. Synthesis and pharmacology. Pharm Weekbl Sci Ed 12:236–239

Leschke C, Elz S, Garbarg M, Schunack W (1995) Synthesis and histamine H_1 receptor agonist activity of a series of 2-phenylhistamines, 2-heteroarylhistamines, and analogues. J Med Chem 38:1287–1294

Leurs R, Smit MJ, Timmerman H (1995) Molecular pharmacological aspects of histamine receptors. Pharmacol Ther 66:413–463

Lipp R, Arrang JM, Garbarg M, Luger P, Schwartz JC, Schunack W (1992a) Synthesis, absolute configuration, stereoselectivity, and receptor selectivity of (αR,βS)-α,β-dimethylhistamine, a novel highly potent histamine H_3 receptor agonist. J Med Chem 35:4434–4441

Lipp R, Stark H, Schunack W (1992b) Pharmacochemistry of H_3-receptors. In: Schwartz J, Haas HL (eds) The histamine receptor. Wiley-Liss, New York, pp 57–72

Malinowska B, Schlicker E (1991) H_3 receptor-mediated inhibition of the neurogenic vasopressor response in pithed rats. Eur J Pharmacol 205:307–310

Malinowska B, Schlicker E (1993a) Identification of endothelial H_1, vascular H_2 and cardiac presynaptic H_3 receptors in the pithed rat. Naunyn-Schmiedeberg's Arch Pharmacol 347:55–60

Malinowska B, Schlicker E (1993b) Effects of H_1, H_2 and H_3 agonists on the neurogenic vasopressor response in the pithed rat. Agents Actions 38 (Spec No):C254–C256

Malinowska B, Schlicker E, Göthert M (1992) Direct and indirect effects of histamine H_1, H_2 and H_3 receptor agonists on blood pressure and heart rate of the pithed rat (abstract). Pol J Pharmacol Pharm [Suppl] 44:91

Nilsson BO, Kockum J, Rosengren E (1997) Effects of aminoguanidine and L-NAME on histamine-induced blood pressure drop in the rat. Acta Physiol Scand 161:339–344

Schwartz JC, Arrang JM, Garbarg M, Pollard H, Ruat M (1991) Histaminergic transmission in the mammalian brain. Physiol Rev 71:1–51

Vollinga RC, Koning JP de, Jansen FP, Leurs R, Menge WMPB, Timmerman H (1994) A new potent and selective histamine H_3 receptor agonist, 4-(1H-imidazol-4-ylmethyl)piperidine. J Med Chem 37:332–333

Zingel V, Elz S, Schunack W (1990) Histamine analogues. 33rd communication: 2-phenylhistamines with high histamine H_1-agonistic activity. Eur J Med Chem 25:673–680

Zingel V, Leschke C, Schunack W (1995) Developments in histamine H_1-receptor agonists. Prog Drug Res 44:49–85