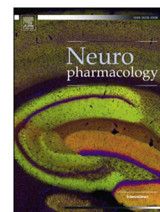
Neuropharmacology 106 (2016) 129–134

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm



A search for presynaptic inhibitory histamine receptors in guinea-pig tissues: Further H_3 receptors but no evidence for H_4 receptors

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ARTICLE INFO

Article history:
Received 30 March 2015
Received in revised form
18 June 2015
Accepted 19 June 2015
Available online 23 July 2015

Keywords:
Histamine H_4 receptor
Histamine H_3 receptor
Guinea-pig atrium
Presynaptic receptor
Noradrenaline release
Acetylcholine release

ABSTRACT

The histamine H_4 receptor is coupled to $G_{i/o}$ proteins and expressed on inflammatory cells and lymphoid tissues; it was suggested that this receptor also occurs in the brain or on peripheral neurones. Since many $G_{i/o}$ protein-coupled receptors, including the H_3 receptor, serve as presynaptic inhibitory receptors, we studied whether the sympathetic neurones supplying four peripheral tissues and the cholinergic neurones in the hippocampus from the guinea-pig are equipped with release-modulating H_4 and H_3 receptors. For this purpose, we preincubated tissue pieces from the aorta, atrium, renal cortex and vas deferens with ^{3}H-noradrenaline and hippocampal slices with ^{3}H-choline and determined the electrically evoked tritium overflow. The stimulation-evoked overflow in the five superfused tissues was inhibited by the muscarinic receptor agonist oxotremorine, which served as a positive control, but not affected by the H_4 receptor agonist 4-methylhistamine. The H_3 receptor agonist *R*-α-methylhistamine inhibited noradrenaline release in the peripheral tissues without affecting acetylcholine release in the hippocampal slices. Thioperamide shifted the concentration–response curve of histamine in the aorta and the renal cortex to the right, yielding apparent pA_2 values of 8.0 and 8.1, respectively, which are close to its affinity at other H_3 receptors but higher by one log unit than its pK_i at the H_4 receptor of the guinea-pig. In conclusion, histamine H_4 receptors could not be identified in five experimental models of the guinea-pig that are suited for the detection of presynaptic inhibitory receptors whereas H_3 receptors could be shown in the peripheral tissues but not in the hippocampus.

This article is part of the Special Issue entitled 'Histamine Receptors'.

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1. Introduction

The H_4 receptor is predominantly expressed on inflammatory cells and lymphoid tissues (for review, see Leurs et al., 2009; Marson, 2011) although its occurrence in the brain has been suggested as well. H_4 receptor mRNA was found in the brain by some but not all investigators (reviewed by Marson, 2011; Schneider et al., 2015). Studies dedicated to the identification of H_4 receptors on the protein level must be assessed critically since in those studies (e.g., Connelly et al., 2009; Lethbridge and Chazot, 2010) H_4 receptor antibodies were used that did not fulfill the stringent criteria for antibodies against G protein-coupled receptors (Michel et al., 2009; Seifert et al., 2013). There is also evidence from functional studies that H_4 receptors may play a role in the CNS, including electrophysiological (Desmadryl et al., 2012; Connelly et al., 2009) and behavioural investigations (Ballerini et al., 2013; Saligrama et al., 2012; Galeotti et al., 2013). A critical appraisal of those studies is given in the review by Schneider and Seifert (2016), appearing in this issue of Neuropharmacology.

Two typical properties of $G_{i/o}$ protein-coupled receptors, namely an increase in ^{35}S-GTPγS binding (Strange, 2010) and an inhibition of exocytotic noradrenaline release (Schlicker and Göthert, 1998), were not shared by H_4 receptor activation on cortical membranes (guinea-pig and mouse) and cortical slices (human, guinea-pig and mouse), respectively, although activation of H_3 receptors, which are $G_{i/o}$ protein-coupled as well (Alexander et al., 2013), elicited both responses (Feliszek et al., 2015). By contrast, not only H_3, but also H_4, receptor activation inhibited noradrenaline release on guinea-pig cardiac synaptosomes in the study by Chan et al. (2012). The aim of the present study was to extend their work in a threefold manner. First, another preparation of the guinea-pig atrium (i.e. isolated tissue pieces) was chosen to confirm the inhibitory effect of H_4 receptor activation. Second, we were interested whether an H_4 receptor-mediated inhibition of noradrenaline release is detectable in another three sympathetically innervated tissues or organs, i.e.

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http://dx.doi.org/10.1016/j.neuropharm.2015.06.020
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the aorta, renal cortex and vas deferens. Third, we examined whether H_4 receptor activation, although not affecting noradrenaline release in the guinea-pig cortex (Feliszek et al., 2015), may inhibit the release of another transmitter, i.e. acetylcholine, in guinea-pig hippocampal slices. The effects of the H_4 receptor agonist 4-methylhistamine and the H_3 receptor agonist *R*-α-methylhistamine were studied in parallel. The muscarinic receptor agonist oxotremorine was used as a positive control since acetylcholine release in the brain and noradrenaline release in sympathetically innervated organs or tissues is strongly inhibited via presynaptic muscarinic auto- (Starke et al., 1989) and heteroreceptors (Boehm and Kubista, 2002; Kurz et al., 2008), respectively.

2. Material and methods

2.1. Superfusion studies

Hippocampal slices (0.3 mm thick, diameter 2 mm) and tissue pieces (approximately 1 × 1 × 1 mm) from the aorta, atrium, renal cortex and vas deferens were prepared from Dunkin-Hartley guinea-pigs (Charles River, Sulzfeld, Germany). Preparations were incubated for 60 min with physiological salt solution (PSS; 37 °C; for composition, see below) containing ^{3}H-noradrenaline (peripheral tissues) or ^{3}H-choline (hippocampal slices; for details, see Table 1). Subsequently, the tissues were superfused at a flow rate of 1 mL/min with PSS (37 °C). The PSS had the following composition (mM): NaCl 118, KCl 4.8, $CaCl_2$ 1.3 (incubation) or 3.25 (superfusion), KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25, ascorbic acid 0.06, disodium EDTA 0.03, glucose 10; the solution was aerated with 95% O_2 and 5% CO_2 (pH 7.4). The superfusate was collected in 5-min samples. The PSS routinely contained an inhibitor of the respective neuronal transporter (desipramine, hemicholinium) to increase the electrically evoked tritium overflow and to avoid interference of test drugs with the respective transporter and an antagonist of the respective autoreceptor (rauwolscine, AF-DX 384) to increase the electrically evoked tritium overflow and its modulation via presynaptic heteroreceptors. Tritium overflow was evoked by two 2-min periods of electrical field stimulation (S_1 and S_2) after 40 and 90 min. Rectangular pulses of 200 mA and 2 ms were administered at a frequency of 3 Hz. The agonist under study (*R*-α-methylhistamine, 4-methylhistamine or oxotremorine in Fig. 1 and histamine in Fig. 2) was present in the medium from 62 min of superfusion onward. The H_3/H_4 receptor antagonist thioperamide (studied on the aorta and renal cortex only; Fig. 2) was present throughout superfusion.

Tritium efflux was calculated as the fraction of the tritium content in the tissues at the beginning of the respective collection period (fractional rate of tritium efflux). To quantify effects of the drugs on basal efflux, the ratio of the fractional rates in the 5 min period from 85 to 90 min (t_2) and in the 5 min period from 55 to 60 min (t_1) was calculated or t_1 was determined in the presence and absence of the drug under study. Stimulation-evoked tritium overflow was calculated by subtraction of basal from total efflux during stimulation and the subsequent 13 min and expressed as per cent of the tritium present in the tissue at the onset of stimulation (basal efflux was assumed to decline linearly from the 5 min period before to that 15–20 min after onset of stimulation). To quantify drug-induced effects on the stimulated tritium overflow, the ratio of the overflow evoked by S_2 over that evoked by S_1 was calculated (S_2/S_1) or S_1 was determined in the presence and absence of the drug under study.

2.2. Drugs and chemicals

[Methyl-^{3}H]-choline chloride (spec. act. 78.3 Ci/mmol), (R)-(−)-[ring-2,5,6-^{3}H]-noradrenaline (spec. act. 48.4 Ci/mmol) (PerkinElmer, Boston, MA, USA); AF-DX 384 (*N*-(2-[(2*R*)-2-[(dipropylamino)methyl]piperidin-1-yl]ethyl)-6-oxo-5*H*-pyrido[2,3-*b*][1,4]benzodiazepine-11-carboxamide) (Boehringer-Ingelheim, Biberach an der Riss, Germany); desipramine hydrochloride, hemicholinium-3, histamine dihydrochloride, oxotremorine sesquifumarate (Sigma, München, Germany); 4-methylhistamine dihydrochloride (Biotrend, Köln, Germany); *R*-α-methylhistamine dihydrogenmaleate (Professor W. Schunack †, Institut für Pharmazie, Freie Universität, Berlin, Germany); rauwolscine hydrochloride (Roth, Karlsruhe, Germany); thioperamide hydrogenmaleate (Schering-Plough Research, Bloomfield, NJ, USA). The other chemicals used were of reagent grade. Stock solutions of the drugs were prepared with dimethyl sulfoxide (thioperamide) or water and diluted with PSS to the concentration required. The solvents did not affect tritium efflux by themselves.

2.3. Statistics and calculations

Results are given as means ± standard error of the mean (SEM) of n experiments. For comparison of mean values, the one-way analysis of variance (ANOVA) followed by the Tukey–Kramer multiple comparisons test was used. To characterize the potency of histamine its EC_{50} (concentration that produces its half-maximum effect, i.e. an inhibition by 25%) was determined; the maximum effect is 50% for the renal cortex and the same value was also assumed for the aorta although the bottom of the concentration–response curve is not so well defined as in the case of the renal cortex. The apparent pA_2 value of thioperamide against histamine was determined according to the formula $pA_2 = \log([A']/[A] - 1) - \log[B]$, where [A'] and [A] are the EC_{50} values for histamine obtained in the presence and absence of thioperamide and [B] represents the concentration of thioperamide (Furchgott, 1972).

3. Results

Experiments were performed on hippocampal slices preincubated with ^{3}H-choline and on four sympathetically innervated

Table 1
Experimental conditions, basal and stimulation-evoked tritium overflow in superfused tissues from the guinea-pig.

Tissue	Tracer	(μM)	Auxiliary drugs (μM)	Basal tritium efflux (t_1)	Electrically evoked tritium overflow (S_1)
Hippocampus	^{3}H-Choline	0.1	Hemicholinium 10 + AF-DX 384 0.1	0.0012 ± 0.0002	2.72 ± 0.31
Aorta	^{3}H-Noradrenaline	0.025	Desipramine 1 + rauwolscine 1	0.0019 ± 0.0002	5.00 ± 0.52
Atrium	^{3}H-Noradrenaline	0.025	Desipramine 1 + rauwolscine 1	0.0024 ± 0.0002	2.05 ± 0.35
Renal cortex	^{3}H-Noradrenaline	0.025	Desipramine 1 + rauwolscine 1	0.0037 ± 0.0004	4.19 ± 0.51
Renal cortex	^{3}H-Noradrenaline	0.1	Desipramine 1 + rauwolscine 1	0.0041 ± 0.0002	3.46 ± 0.15
Vas deferens	^{3}H-Noradrenaline	0.025	Desipramine 1 + rauwolscine 1	0.0015 ± 0.0002	3.67 ± 0.54

Basal tritium efflux (t_1) was expressed as the fractional rate of tritium efflux (min^{-1}) in the collection period from 55 to 60 min.
Tritium overflow evoked by the first period of electrical stimulation (S_1, after 40 min of superfusion) was expressed as percent of tissue tritium.
Means ± SEM of 8 experiments.

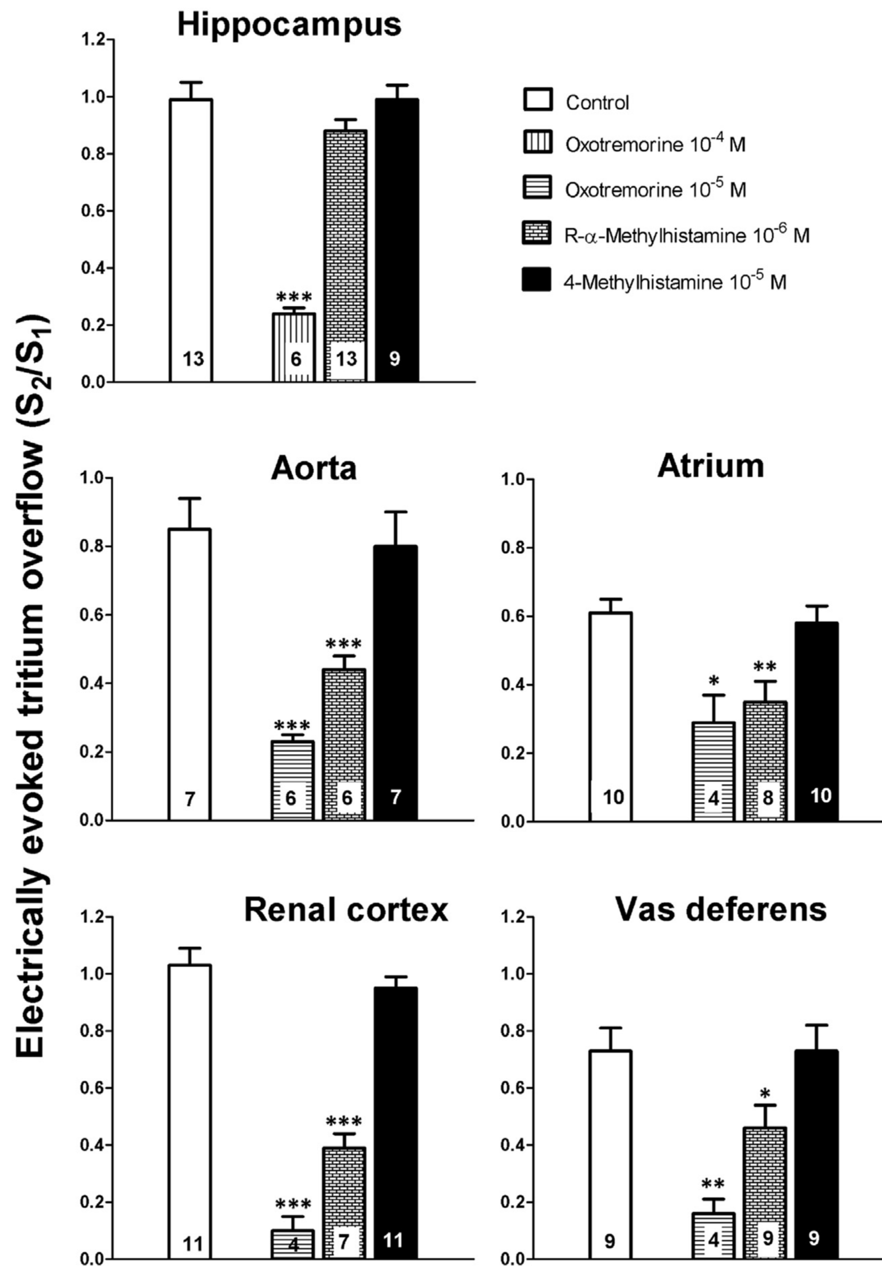

Fig. 1. Effect of *R*-α-methylhistamine, 4-methylhistamine and oxotremorine on the electrically (3 Hz) evoked tritium overflow from superfused guinea-pig tissues. Hippocampal slices preincubated with ^{3}H-choline 0.1 μM and tissue pieces from the aorta, atrium, renal cortex and vas deferens preincubated with ^{3}H-noradrenaline 0.025 μM were studied. The three agonists were used at concentrations known to lead to maximum responses at their respective receptors. To have comparable conditions between the hippocampus and the peripheral tissues oxotremorine had to be administered at a tenfold higher concentration in the hippocampus since the muscarinic receptor antagonist AF-DX 384 0.1 μM, which leads to a tenfold rightward shift of the concentration–response curve of oxotremorine (Schulte et al., 2012), was routinely present in the experiments on the hippocampal slices. Tritium overflow was evoked after 40 and 90 min of superfusion (S_1, S_2), and the ratio of the overflow evoked by S_2 over that evoked by S_1 was formed. The drug under study was added to the medium from 62 min of superfusion onward. Means ± SEM of the number of experiments indicated in the columns. Results were statistically evaluated by ANOVA ($P < 0.001$ for each of the 5 panels) followed by the Tukey–Kramer multiple comparisons test. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

periperal organs or tissues preincubated with ^{3}H-noradrenaline. Basal tritium efflux was expressed as t_1 or t_2/t_1 (see Methods). The t_1 values in controls are given in Table 1; they were not affected by thioperamide 0.1 μM (not shown). The t_2/t_1 value was close to 0.8 in control experiments and not affected by the drugs under study (not shown). The electrically evoked tritium overflow was expressed as S_1 or S_2/S_1 (see Methods). Control values are given in Table 1 (S_1) and in Fig. 1 and the legend to Fig. 2 (S_2/S_1). The effects of the test drugs were examined in two experimental series shown in Figs. 1 and 2.

In the first series, the effect of the histamine H_3 receptor agonist *R*-α-methylhistamine and the H_4 receptor agonist 4-methylhistamine on the electrically evoked tritium overflow (S_2/S_1) was studied on hippocampal slices and sympathetically innervated organs or tissues. The muscarinic receptor agonist oxotremorine served as a positive control. The three drugs were administered at concentrations that elicit the maximum effect at the respective receptors. *R*-α-Methylhistamine inhibited the electrically evoked tritium overflow in tissue pieces from the aorta, atrium, renal cortex and vas deferens without affecting that in hippocampal slices (Fig. 1). 4-Methylhistamine failed to alter the evoked overflow whereas oxotremorine strongly inhibited it in each of the five tissues (Fig. 1).

The second series of experiments was dedicated to the H_3

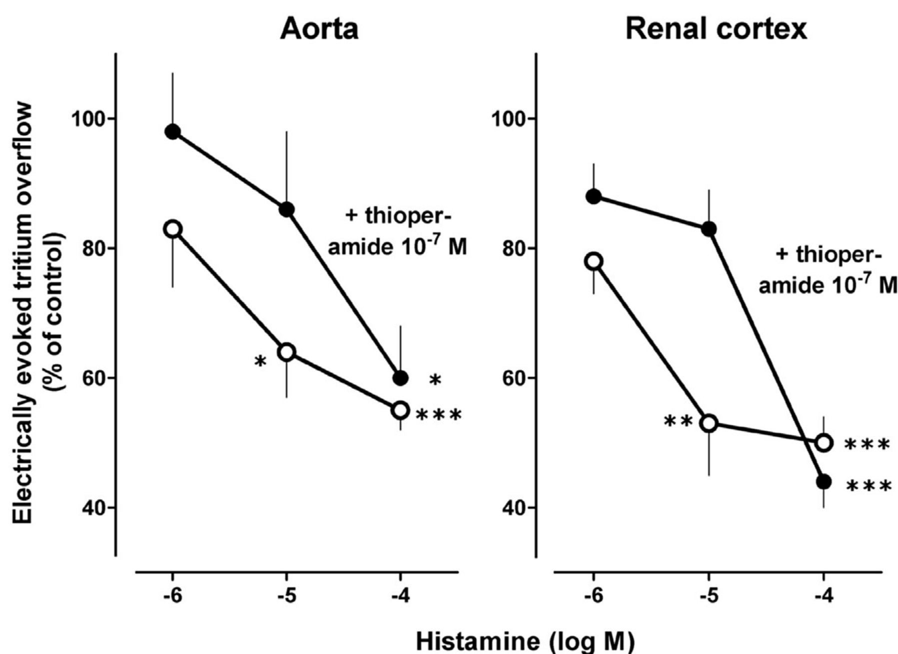

Fig. 2. Effect of histamine on the electrically (3 Hz) evoked tritium overflow from superfused guinea-pig tissues and interaction with thioperamide. Tissues from the aorta and renal cortex preincubated with ^{3}H-noradrenaline 0.025 and 0.1 μM were studied, respectively. Tritium overflow was evoked after 40 and 90 min of superfusion (S_1, S_2), and the ratio of the overflow evoked by S_2 over that evoked by S_1 was formed. Histamine was added to the medium from 62 min of superfusion onward whereas thioperamide was present throughout superfusion. Tritium overflow is expressed as percent of the S_2/S_1 value in the corresponding histamine-free control; control S_2/S_1 values were 0.75 ± 0.05 (aorta, no thioperamide), 0.65 ± 0.05 (aorta, thioperamide 0.1 μM), 0.91 ± 0.05 (renal cortex, no thioperamide) and 1.04 ± 0.03 (renal cortex, thioperamide 0.1 μM). Means ± SEM of 4–5 (aorta) and 7–8 experiments (renal cortex). Results were statistically evaluated by ANOVA ($P < 0.001$, except for aorta + thioperamide with $P < 0.05$) followed by the Tukey–Kramer multiple comparisons test.*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, compared to the histamine-free control (not shown).

receptors on the sympathetic neurones innervating the aorta and renal cortex. For this purpose, the interaction of histamine with thioperamide was examined. Histamine inhibited the electrically evoked tritium overflow (S_2/S_1) in the aorta and renal cortex in a concentration-dependent manner (Fig. 2). The maximum inhibitory effect of histamine was close to 50% in either tissue and its potency (pEC_{50}) was 5.6 (aorta) and 5.9 (renal cortex). The concentration–response curve of histamine was shifted to the right by thioperamide 0.1 μM (Fig. 2), yielding apparent pA_2 values of 8.0 (aorta) and 8.1 (renal cortex). Thioperamide 0.1 μM did not affect the evoked tritium overflow (S_1) by itself (results not shown).

4. Discussion

This study, dedicated to histamine H_3 and H_4 receptors, was carried out on superfused tissues preincubated with ^{3}H-choline or ^{3}H-noradrenaline; electrical stimulation was used to elicit quasi-physiological exocytotic release of the respective transmitter. Since inhibition of transmitter release by $G_{i/o}$ protein-coupled receptors (to which H_3 and H_4 receptors belong) can be improved by the simultaneous blockade of the muscarinic (Hiramatsu et al., 1998; Nishiwaki et al., 1998; Giaroni et al., 1999; Shakirzyanova et al., 2006) or α_2-autoreceptor (for review, see Schlicker and Göthert, 1998) AF-DX 384 and rauwolscine were used in our experiments, respectively. Since it was unclear whether H_3 and H_4 receptors can be detected in each of the five experimental models, the muscarinic receptor agonist oxotremorine was studied as a positive control. This drug elicits its maximum inhibitory effect at 10 μM on sympathetically innervated tissues (Kurz et al., 2008). In hippocampal slices, oxotremorine had to be administered at a tenfold higher concentration since those experiments were routinely carried out in the presence of AF-DX 384 (Schulte et al., 2012). As expected, oxotremorine led to a marked inhibition of transmitter release in each of the five experimental models, clearly demonstrating that modulation of transmitter release by presynaptic inhibitory receptors is possible under the experimental conditions of the present study.

The H_4 receptor agonist 4-methylhistamine (Lim et al., 2005) was used at a concentration (10 μM) that exceeds its K_i value at the gpH_4 receptor by a factor of 200 (Lim et al., 2010) and was close to the concentration (20 μM) used on guinea-pig cardiac synaptosomes by Chan et al. (2012). 4-Methylhistamine did not affect transmitter release in the release models of our study, including the heart. In the latter preparation, the H_3 agonist *R*-α-methylhistamine (Arrang et al., 1987), used at a concentration (1 μM) that elicits the maximum effect at functional H_3 receptors of the guinea-pig (Luo and Tan, 1994; Timm et al., 1998), did inhibit noradrenaline release. The reason why the cardiac synaptosome preparation allowed the identification of H_3 *and* H_4 receptors whereas only the H_3 receptor could be identified on the isolated atrium is unclear. Presynaptic cardiac H_3 receptors, first shown by Luo et al. (1991) on electrically stimulated atrial strips of the guinea-pig, have also been showed on the human (Imamura et al., 1995) and rat atrium (Malinowska and Schlicker, 1993).

R-α-Methylhistamine inhibited noradrenaline release also in the aorta, renal cortex and vas deferens. The presynaptic H_3 receptor on the guinea-pig vas deferens has been shown for the first time by Luo and Tan (1994), who examined the electrically induced contractile response instead of directly quantifying noradrenaline release. The occurrence of H_3 receptors has also been suggested for the guinea-pig aorta in vitro (Schultheiß et al., 2005) and the dog kidney in vivo (Yamasaki et al., 2001). Since the latter two studies are, however, based on single concentrations or doses of H_3 receptor ligands only, additional experiments based on whole concentration–response curves were carried out in the aorta and renal cortex.

Thioperamide, which possesses a high preference for H_3 over H_1 or H_2 receptors (Arrang et al., 1987; Hough, 2001), served as the antagonist. Although it does not discriminate well between H_3 and H_4 receptors (Hough, 2001) it was used anyway since affinity data

for each of the four histamine receptor subtypes in guinea-pig tissues are available. Its apparent pA_2 value of 8.0–8.1 in our interaction experiments agreed well with its pA_2 in other functional H_3 receptor models of the guinea-pig (8.1–8.2; Timm et al., 1998; Feliszek et al., 2015) but exceeded its affinity (pK_i) at H_4 receptors (7.1; Lim et al., 2010) markedly and its affinity at H_1 ($pK_B < 4$; Arrang et al., 1987) and H_2 receptors ($pK_B < 5$; Arrang et al., 1987) extremely. These data allow us to conclude that the inhibitory presynaptic histamine receptor in the aorta and renal cortex is indeed an H_3 receptor.

Histamine, which was used as the agonist, had low potencies in our functional experiments when compared to its affinity from binding studies (e.g. Lim et al., 2005). This phenomenon is related to the fact that the coupling of the presynaptic receptor to the transduction machinery and the final functional response is impaired due to the experimental conditions including the stimulation protocol. This can be shown if one e.g. compares the potency of histamine for the H_3 receptor-mediated inhibition of noradrenaline release in guinea-pig peripheral tissues (pEC_{50} of 5.6 in the aorta and of 5.9 in the kidney; present study) and cerebral cortex slices (pEC_{50} of 6.5; Timm et al., 1998). In the latter study, a lower stimulation frequency (0.3 vs. 3 Hz) and a lower Ca^{2+} concentration (1.3 vs. 3.25 mM) could be used, both of which are associated with an improved effect mediated via presynaptic receptors (Starke, 1977).

Acetylcholine release from hippocampal slices was not affected by *R*-α-methylhistamine and this finding is in harmony with previous studies on hippocampal slices from the rat (Alves-Rodrigues et al., 1998). On slices of another brain region of the rat, the entorhinal cortex, an inhibitory effect was obtained (Clapham and Kilpatrick, 1992), which, however, did not occur on synaptosomes, i.e. isolated nerve endings (Arrang et al., 1995). The latter data suggest that the H_3 receptor cannot be located on the cholinergic nerve endings themselves but must be located on an interneurone. This phenomenon may also explain why H_3 receptor activation in various brain regions of the rat in vivo can even increase acetylcholine release (e.g. Passani et al., 2001; Cangioli et al., 2002) although an inhibition was observed as well (e.g. Ligneau et al., 2007; Munari et al., 2013).

In conclusion, using superfused atrial tissue pieces we could not detect the histamine H_4 receptor suggested by Chan et al. (2012) on the basis of experiments on synaptosomes from the same tissue. This receptor could also not been found in another four superfusion models of the present study (aorta, renal cortex, vas deferens, hippocampus) and in the superfused cerebral cortex of humans, guinea-pigs and mice in our previous paper (Feliszek et al., 2015). H_3 receptors although not detected in the hippocampus could be shown in the atrium, vas deferens, aorta and renal cortex and for the latter two tissues the involvement of this receptor could be proven by an interaction study with thioperamide.

Acknowledgements

This work was supported by the “BONFOR” programme of the Medical Faculty of the University of Bonn. We would like to thank Boehringer-Ingelheim and Schering-Plough Research for gifts of AF-DX 384 and thioperamide, respectively. *R*-α-Methylhistamine has been kindly donated by Professor Walter Schunack (deceased on April 6, 2011), who has supported the work of this group on numerous occasions.

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