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Evidence of a dual role of endogenous histamine in angiogenesis*

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Summary. The specific activation of mast cells *in situ* causes vigorous local mast-cell mediated angiogenesis (MCMA). The mast cell is a major source of histamine and, as recently reported, specific histamine H_1- and H_2-membrane receptor antagonists are able individually to significantly suppress MCMA in rats, as assessed using the mesenteric window angiogenesis assay (MWAA). In addition to membrane receptors for histamine, a type of intracellular histamine receptors, designated H_{ic}, has been described. It is now demonstrated that the potent H_{ic}-receptor antagonist DPPE (*N*,*N*-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine HCl), administered parenterally, stimulates MCMA significantly in rats, as quantified by the MWAA. Although the target cell(s) are not known, there are several ways by which their H_{ic} receptors could be activated: uptake of histamine released from mast cells, mobilization from preformed cytoplasmic and nuclear stores, and production of *de novo* histamine by histidine decarboxylase activity. The fact that the occupancy by histamine of H_1- and H_2-membrane receptors stimulates MCMA and the occupancy by histamine of H_{ic} inhibits MCMA suggests that endogenous histamine is capable of regulating angiogenesis by a dual mode of action. This is apparently the first report ascribing a dual role of this type in angiogenesis to a single molecule.

Keywords: histamine, intracellular receptor, neovascularization, mast cells, rat, mesentery, quantification

Histamine has been associated with normal tissue cell multiplication both as an intracellular mediator, following increased intracellular histidine decarboxylase activity in proliferating cells (Kahlson *et al.* 1963; Brandes *et al.* 1991b; Dy *et al.* 1993), and as a paracrine mitogen, acting through H_2-membrane receptors, following mast-cell secretion *in situ* (Franzén & Norrby 1980; Norrby 1980). Studies of the effect of H_1- and H_2-membrane receptor antagonists in certain tumours have, moreover, indicated that histamine is able to promote neoplastic growth, in addition to modulating immunoreactive cells (Beer *et al.* 1984; Hellstrand & Hermodsson 1986; Nielsen & Kikuchi 1993; Suonio *et al.* 1993). Recently, it was reported that released mast-cell histamine stimulates neovascularization through H_1- and H_2-receptors on as yet unknown target cells in normal healthy rats (Sörbo *et al.* 1994). In addition to membrane receptors for histamine, intracellular histamine receptors, designated H_{ic}, have been reported. A potent and reportedly specific antagonist to H_{ic} is *N*,*N*-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine HCl (DPPE) (Brandes *et al.* 1991b,c; 1992b). The aim of the present paper was to study the effect of DPPE on *de novo*

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mast-cell mediated angiogenesis (MCMA) in normal adult rats. The mesenteric window angiogenesis assay (MWAA) was used for quantitative assessment.

Material and methods

Animals

Adult male Sprague–Dawly rats (B & K Universal, Sollentuna, Sweden), weighing a mean of 255 g at the start of the experiment, were used. The rats were acclimatized to the standardized conditions of our animal room for $\geqslant$ 5 days before the start of the experiment (Norrby *et al.* 1986). The animals were allocated at random to weight matched groups and their weights were monitored throughout the experiment. Two rats shared each cage and they were fed water and standard pellets freely.

The mesenteric window used for measuring angiogenesis

The tissue which was used is the mebranous, 'window'-like parts of the true mesentery. This adult tissue is normally vascularized and appears to lack significant physiologic angiogenesis (Norrby *et al.* 1986; 1990). SInce the mesenteric windows natively measure only 5–10 μm in thickness, the vasculature is virtually two-dimensional. In avascular parts, fibroblasts and mesothelial cells each constitute some 46–48% of all the tissue-bound cells, whereas mast cells and macrophages each make up approximately 1.5–2.5 and 1–2% (Norrby & Enestrom 1984). The mast cell is the major, if not the only, source of histamine in this tissue. Due to the structural and metabolic simplicity of the test tissue, the mesenteric window microvasculature is regarded as an ideal test system for establishing the functional influences of defined factors (Zweifach 1973).

Induction of mast-cell mediated angiogenesis

The highly selective, archetypal mast-cell secretagogue compound 48/80 (Sigma) was dissolved and diluted in saline for infusion (0.9% NaCl, w/v; Kabi Pharmacia); 2 ml/100 g b.w. was injected i.p. twice daily for 4.5 consecutive days according to a previously described protocol (Norrby *et al.* 1986). The treatment causes an angiogenic reaction of long duration which is, in fact, greater and of longer duration than the angiogenic response induced by basic fibroblast growth factor (Norrby 1994).

The subcutaneous administration of the H_{ic}-receptor antagonist DPPE

DPPE (Brandes & Hermonat 1984), dissolved in saline and sterilized by Millipore filtration, was injected (0.10 ml/100 g b.w.) s.c. in the back at doses of 1 and 4 mg/kg in two groups, each comprising 10 animals. Ten controls received saline s.c. instead of DPPE. The injections of DPPE and saline were given 1 hour before each i.p. injection of 48/80.

DPPE injected s.c. at a dose of 2 mg/kg was also given alone twice daily for 4.5 consecutive days to check whether this treatment by itself induced angiogenesis in the mesenteric window in animals not receiving i.p. treatment with 48/80; controls received saline s.c.

DPPE is known to bind to two distinct H_{ic} subtypes: a single species of low-affinity, high-capacity sites associated with the microsomal fraction (Brandes *et al.* 1990) and both low and high-affinity sites in the nuclear fraction (Brandes *et al.* 1991b); both H_{ic} subtypes appear closely associated with anti-oestrogen binding sites (Brandes *et al.* 1992b). DPPE is reported to be a specific antagonist to H_{ic} (Brandes *et al.* 1991b).

Quantification of angiogenesis in microtome sections

Angiogenesis was quantified by microscopically counting the number of vessel profiles per unit length of the mesenteric window (No/UL) in four microtome sections per specimen, cut perpendicularly to the surface, from a central part of the window (Norrby 1994). No/UL indirectly reflects the degree of branching, the degree of tortuosity and the degree of spatial expansion of the vasculature. Four specimens per animal were analysed. The reproducibility of this technique was very high, $r \geqslant 0.99$, using linear regression analysis of repeated counts made at different times.

Quantification of angiogenesis in spreads of intact mesenteric window

The relative vascularized area (VA). Whole medium-sized windows, spread and fixed on objective slides and subsequently stained with toluidine blue, were used to measure VA by microscopic and morphometric means according to recently described criteria (Norrby 1994). SInce the vasculature is virtually two-dimensional in the thin test tissue, VA is in practical terms a measure of the spatial extension of the vasculature. Four mesenteric window specimens were analysed per animal.

The microvascular length (MVL). Whenever available,

Table 1. Effect of DPPE on mast-cell secretion in terms of histamine release following i.p. injections of compound 48/80

Treatment	*n*	Histamine base/protein Mean ± s.e.m.	Percentage release
Untreated control	6	2.092 ± 0.149	–
48/80 i.p. + saline s.c.	10	0.788 ± 0.019	62
48/80 i.p. + DPPE 1 mg/kg s.c.	10	0.733 ± 0.033	65
48/80 i.p. + DPPE 4 mg/kg s.c.	10	0.772 ± 0.36	63

No significant difference was found between the saline and the DPPE treated animals in statistical terms.
n, Number of animals.

three systematically randomly selected vascularized view fields per mesenteric-window spread were analysed using microscopy and image analysis as described elsewhere (Norrby 1994). MVL, a measure of the vessel length per unit area of vascularized tissue, reflects the degree of branching and tortuosity of the vessels. The numbers of specimens permitting three view fields to be analysed for MVL according to these criteria were 37 for saline controls, 40 for animals receiving DPPE at 1 mg/kg and 15 for those receiving DPPE at 4 mg/kg. The level of reproducibility when measuring VA and MVL was very high (using linear regression analysis, $r \geqslant 0.98$).

The total microvascular length (TMVL) was computed from the VA of each animal multiplied by the mean (or percentage mean) MVL for the corresponding treatment group. TMVL is a measure of the total vessel length per mesenteric window.

Histamine release as a marker of mast-cell secretion

Compound 48/80 (1 μg/g, 2 ml/100 g b.w.) was given i.p. at 0800 h on two consecutive days and the animals were killed 1 hour after the second injection. Three randomly selected, medium sized mesenteric windows per animal were excised, pooled, immediately frozen and stored at −70°C. Histamine was quantified by a fluorometric OPT-reaction (Enerbäck & Wingren 1980) and the total protein was quantified according to Lowry *et al.* (1951); the histamine content was expressed as ng histamine base per μg protein.

Statistics

The non-parametric two-tailed Mann-Whitney *U* rank sum test for unpaired observations was used. The criterion for statistical significance was a probability value $P \leqslant 0.05$. For No/UL, VA and TMVL, the means of four windows per animal were used as independent data, whereas the means of three view fields per specimen were used as independent data for MVL.

Results

The animals receiving the s.c. DPPE or saline treatment appeared to be normal in all respects. No inflammatory reaction was observed with the naked eye, nor was any ulceration seen at the s.c. injection sites. No animal died during the experiment.

Effect of DPPE on normal body weight gain

DPPE given s.c. did not affect the body weight compared with controls receiving saline injections s.c. despite the fact that the animals gained some 36% in weight during the experimental period. At sacrifice, the mean (± s.e.m.) body weight was 346.00 ± 4.88 for the controls and 347.10 ± 3.20 or 346.90 ± 3.64 for the animals receiving treatment with DPPE at doses of 1 or 4 mg/kg.

Effect of DPPE on mast-cell secretion in terms of histamine release

The i.p. treatment with compound 48/80 released approximately 65% of the histamine present in the native test tissue. The s.c. treatment with DPPE at doses of 1 or 4 mg/kg did not significantly affect the degree of histamine released in the mesenteric window following the treatment with 48/80 compared with the controls receiving saline s.c. (Table 1).

Effect of DPPE on mast-cell mediated angiogenesis

The DPPE treatment s.c. at 1 or 4 mg/kg increased angiogenesis in the mesenteric windows in terms of No/UL by almost 50%, VA by 24–25%, MVL by 7–8% and TMVL by 34%. The increase in No/UL, VA and TMVL was significant in statistical terms compared with the saline treated controls (Tables 2 and 3; Figure 1).

As expected, the s.c. injection of DPPE at 2 mg/kg in animals that did not receive any i.p. angiogenic treatment did not cause angiogenesis in the mesenteric window test tissue compared with controls receiving saline s.c. (data not shown).

Discussion

The present finding that a potent antagonist to intra-

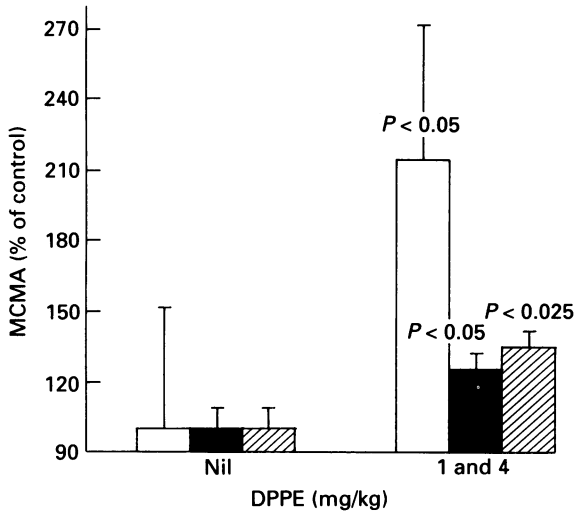

Figure 1. Effect of DPPE on mast-cell mediated angiogenesis (MCMA) in terms of □, No/UL; ■, VA and ▨,TMVL (data derived from Tables 2 and 3). The data from animals receiving the agent s.c. at 1 or 4 mg/kg were combined; there were thus 20 DPPE treated animals and 10 controls per group. Means ± s.e.m. *P*-values refer to differences between DPPE and saline treated animals.

cellular histamine receptors, H_{ic}, stimulated mast-cell mediated angiogenesis (MCMA) is new and suggests that endogenous histamine suppressed MCMA by occupying H_{ic}. Angiogenesis was quantified by technically independent variables which were measured with a very high degree of reproducibility and accuracy. No/UL, VA and TMVL were statistically significantly increased in the DPPE treated animals. As no intravascular marker was used for the visualization of the microvasculature, no possible differences in the intravascular pressure at fixation between treatment groups could have influenced the results. The fact that the DPPE treatment did not affect normal body weight gain suggests that the agent was not toxic at the doses used. Recently, it was reported that specific histamine H_1- and H_2-receptor blockers are able individually to significantly suppress rat MCMA in the same vascular bed, thus indicating the stimulatory effect of histamine when bound to these membrane receptors (Sörbo *et al.* 1994). The H_1- and H_2-membrane receptor blockers and the antagonist to intracellular histamine receptors used here, which were all administered at the same time relative to the angiogenic i.p. treatment given, apparently targeted the expanding microvasculature. Although the target cells still remain to be identified, these two sets of observation suggest the operation of a novel mechanism by which endogenous histamine is able to exert both pro and anti-angiogenic regulatory action in normal adult mammalian tissue.

Table 2. Effect of DPPE on mast-cell mediated angiogenesis in terms of the number of vessel profiles per unit tissue length (No/UL)

	No/UL	
Treatment s.c.	Mean ± s.e.m.	(%)
Saline	68.6 ± 35.3	(100)
DPPE (1 mg/kg)	145.7 ± 46.2	(212)
DPPE (4 mg/kg)	148.1 ± 65.4	(226)

Each treatment group comprised 10 animals. The combined data of animals treated with 1 or 4 mg DPPE per kg increased No/UL by a mean of 114% which was statistically significant compared with the saline treated controls ($P \leqslant 0.05$).

DPPE binds to microsomal and nuclear chromatin sites and is reported to be a potent and specific antagonist to H_{ic} (Brandes *et al.* 1991b; 1992b) although the precise degree of specificity apparently remains to be established. The activation of H_{ic} is often considered to follow the mobilization of preformed cytoplasmic and nuclear histamine or the generation of new histamine by increased histidine decarboxylase activity (Brandes *et al.* 1991b; 1992b). It is moreover known that mast-cell activation is followed by an increase in histidine decarboxylase activity in tissues. As an alternative to the intracellular mobilization and/or synthesis of histamine, released mast-cell histamine could be actively incorporated into target cells by various pathways (Haddock *et al.* 1990), with the chance of activating H_{ic}. The uptake of histamine by many cell types *in vitro* and *in vivo* has been reported. They include platelets (DaPrada & Pletscher 1969), myeloblasts and promyelocytes (Nakaya & Tasaka 1988), leucocytes (Assem 1982; Catini *et al.* 1990), gastric mucosal cells (Albinus & Sewing 1981; Wollin 1990), glial cells (Huszti *et al.* 1990), rat vascular tissue (Holcslaw *et al.* 1984) and endothelial cells (Valen *et al.* 1994).

It is interesting to note that DPPE has recently been demonstrated to stimulate the growth of a DMBA-induced mammary carcinoma in Sprague–Dawley rats and the L5178Y leukaemia when growing in solid nodules in DBA/2 mice (Brandes *et al.* 1991a). Moreover, tricyclic antidepressants with a chemical structure resembling that of DPPE, and which bind to intracellular histamine receptors associated with anti-oestrogen binding sites in microsomes and nuclei, stimulate the growth of solid rodent cancers, viz. the C-3 fibrosarcoma in C3H mice, the B16f10 melonama in C57Bl mice and the DMBA induced mammary carcinoma in Sprague–Dawley rats (Brandes *et al.* 1992a). The tumour stimulating action of DPPE and the DPPE-like antidepressants in

Table 3. Effect of DPPE on mast-cell mediated angiogenesis in terms of vascularized area (VA), microvascular length (MVL) and total microvascular length (TMVL)

	VA	MVL	TMVL
Treatment i.p.	Mean ± s.e.m. (%)	Mean ± s.e.m. (%)	Mean ± s.e.m. (%)
Saline	33.14 ± 2.96 (100)	1.65 ± 0.08 (100)	3314 ± 296 (100)
DPPE (1 mg/kg)	41.22 ± 2.41 (124)	1.78 ± 0.10 (108)	4452 ± 260 (134)
DPPE (4 mg/kg)	41.43 ± 4.21 (125)	1.76 ± 0.05 (107)	4433 ± 451 (134)

Each treatment group comprised 10 animals. The treatment with 1 mg of DPPE per kg increased the VA and TMVL significantly in statistical terms ($P \leqslant 0.05$ and $P \leqslant 0.02$) compared with the saline treated controls. The combined data of 1 or 4 mg of DPPE per kg also increased the VA and TMVL significantly compared with the controls ($P \leqslant 0.05$ and $P \leqslant 0.025$). In terms of MVL, no statistically significant difference was, however, found between any two treatment groups or between the combined groups of DPPE treatment animals compared with the controls.

rats and mice is intriguing in the light of the present finding that DPPE stimulates MCMA in rats, as it is known that tumour angiogenesis is a factor governing the growth rate of solid tumours (Folkman 1990). In tumours, angiogenic factors are apparently produced by the neoplastic cells, as well as by activated stromal cells including mast cells, macrophages and possibly other inflammatory cells. As the activation of mast cells appears to occur regularly in the periphery of tumours and in inflammation (Meininger & Zetter 1992; Norrby & Woolley 1993) MCMA may be a factor in many angiogenesis diseases including solid tumours.

The markedly suppressed generation of prostaglandins and leukotrienes in rats by mepacrine and indomethacin given s.c. or i.v. does not significantly affect either MCMA (unpublished data) or mast-cell mediated mitogenesis (Norrby & Andersson 1984) in the test tissue used here. This suggests that MCMA is not significantly affected by these mediators, which is noteworthy as DPPE can influence the levels of certain prostaglandins in rats and mice (Glavin & Gerrard 1990; Brandes *et al.* 1991c).

In the present study, DPPE was administered concomitantly to the mast-cell activating angiogenic treatment and the results suggest that histamine hampered angiogenesis by occupying H_{1c}. As previously mentioned, this intracellular mode of histamine action together with the angiogenesis stimulating effect of extracellular histamine through H_1- and H_2-membrane receptors (Sörbo *et al.* 1994) indicate that there is a dichotomous angiogenesis controlling mechanism for endogenous histamine; a dual mechanism of this kind has not previously been demonstrated for any single molecule. A postulated mechanism of this type would provide the means for the sensitive regulation of angiogenesis. Additional studies identifying the target cells and the source of histamine binding to the intracellular histamine receptors are needed to elucidate this question further.

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