the saline-treated cortex was 1.09 ± 0.08 pmoles/100 mg protein, whereas in the Mg-pretreated cortex, $1.25 + 0.09$ pmoles/100 mg protein was detected. To demonstrate the Mg^{2+}-facilitation effect in the same animal, an additional series of experiments was undertaken in which 2.1 M K^+-induced cAMP elevation in both normal and Mg-treated hemicortices were performed in the same animal. The following values have been obtained: 4.88 ± 0.67 and 9.03 ± 0.53 pmoles/100 mg protein for saline and Mg^{2+}-pretreated hemicortices respectively.

According to current hypotheses, depolarizing agents, including K^+, act on the cAMP-generating system indirectly, i.e. through adenylate cyclase-linked receptors activated by adenosine and glutamate released from the cells by depolarization[6-8]. Our results demonstrate, however, that potassium ions are able to stimulate cAMP formation independently of their ability to evoke SD, i.e. to induce a massive depolarization of the cortical cells. This might suggest that K^+ stimulates synthesis of cAMP in a direct way, besides that mediated by depolarization. The apparent facilitation effect of magnesium ions on the K^+-induced elevation of cAMP is difficult to explain as yet and remains to be elucidated by further experiments.

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Occurrence of inhibitory histamine H_2-receptors in isolated pulmonary blood vessels of dogs and rats

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Summary. Isolated, helically cut strips of pulmonary arteries and veins of dogs, and pulmonary arteries of rats, precontracted with norepinephrine or 5-HT exhibited potent concentration-dependent relaxations to impromidine and dimaprit (histamine H_2-agonists). The occurrence of inhibitory histamine H_2-receptors in the pulmonary vasculature could play a modulatory role in hypoxic pulmonary vasoconstriction.

It has been firmly established that histamine acts on at least 2 subtypes of receptors, namely H_1 and H_2-receptors, which may act in opposite or similar directions in the cardiovascular, respiratory and gastro-intestinal systems[2]. A dual histamine receptor population (H_1: vasoconstriction; H_2: vasodilatation) is thought to exist in the intact pulmonary circulation of guinea-pigs, dogs and cats[3]. Although a modulatory role for histamine H_2-receptors in hypoxic pulmonary vasoconstriction (HPV) has been hypothesized, at least in dogs, cats and rats[4], the exact anatomical site(s) of these histamine H_2-receptors in the pulmonary vasculature is not as yet known. In this report, we now demonstrate a potent relaxant effect of impromidine and dimaprit (2 highly specific and potent H_2-receptor agonists)[5], on isolated pulmonary blood vessels of rats and dogs.

Material and methods. Helically cut strips of pulmonary arteries and veins were prepared after sacrifice[6] from 10 adult mongrel dogs (12–22 kg), of either sex, and 15 male Wistar rats (300–450 g). The tissues were set up isometrically in isolated tissue baths containing Krebs-Ringer bicarbonate solution[6,7]. The tissues were aerated with a 5% CO_2–95% O_2 mixture, at 37 °C, under a resting load of 2 g for canine pulmonary arterial and venous strips ($2–3 \times 25–30$ mm) and 1 g for rat pulmonary arterial strips (1.5×20 mm). After 2 h of equilibration, the tissues were partially contracted with $ED_{40} \pm 10\%$ concentrations of norepinephrine bitartrate (NE) (50–100 ng/ml) or serotonin creatinine sulfate (5-HT: 10–20 ng/ml) in the case of the canine vessels; for the rat pulmonary artery 0.1–1.0 µg/ml of NE and 1–5 µg/ml of 5-HT were utilized. Responses to single or cumulative doses of impromidine and dimaprit were then recorded in duplicate. After washing and restoration of baseline tension, the agonists were then tested in the presence of the H_2-receptor antagonist, metiamide. Grass FT.03C force transducers and 4-channel Model 5 or 7 polygraphs were utilized, as described previously[7]. Where appropriate, means ± SEMs were calculated and compared for statistical significance by Student's t-test.

Results. The representative data shown in figures 1 and 2, as well as in the table, clearly demonstrate the inhibitory effects of dimaprit and impromidine on isolated pulmonary arteries and veins of dogs ($n = 10$) and rat pulmonary arteries. In general, impromidine is about 100 times more potent as a relaxant han dimaprit when ED_{50} concentrations are compared (table). In addition, impromidine produced a greater maximal relaxation than dimaprit (table).

Other experiments indicated (8 rats and 5 dogs) that metiamide (5×10^{-6} M), a specific H_2-receptor antagonist[2], failed to alter contractile responses to NE or 5-HT. However, metiamide competitively antagonized relaxant responses of both dimaprit and impromidine (e.g., figure 2; dose ratio = 2–5).

Discussion. Histamine is contained in relatively large concentrations in the lungs of rats and dogs as well as of other mammals. Histamine has been considered as a mediator, as well as a modulator of HPV[4], i.e., its exact role in HPV is still not known. Histamine is well-known to induce H_1-receptor-mediated pulmonary vasoconstriction in several mammalian species so far investigated[2]. However, under the conditions of increased pulmonary vascular tone, such as in HPV, histamine may induce pulmonary vasodilatation. Rat pulmonary arteries are relatively insensitive to the contractile action to histamine[6], but, as shown here, exhibit potent, dose-dependent relaxations to H_2-agonists. Thus, there appears to be a preponderance of H_2-inhibitory receptors in rat pulmonary arteries. On the other hand, canine pulmonary blood vessels possess an abundance of H_1-receptors, which are susceptible to blockade by

Comparative sensitivity of isolated intrapulmonary arteries of dogs and rats to dimaprit and impromidine (H_2-agonists)

Agonist	N	Threshold concentration (M) (mean ± SEM)	ED_{50} (M) (mean ± SEM)	Maximal relaxant response (mg) (mean ± SEM)
Canine pulmonary arteries				
Dimaprit	7	$8.63 \pm 2.8 \times 10^{-5}$	$2.91 \pm 0.68 \times 10^{-4}$	390 ± 20
Impromidine	5	$1.34 \pm 1.1 \times 10^{-7}$*	$2.3 \pm 0.57 \times 10^{-6}$*	650 ± 30*
Rat pulmonary arteries				
Dimaprit	7	$9.2 \pm 3.7 \times 10^{-5}$	$3.9 \pm 1.2 \times 10^{-4}$	150 ± 10
Impromidine	8	$3.7 \pm 1.6 \times 10^{-7}$*	$3.8 \pm 0.9 \times 10^{-6}$*	220 ± 15*

* Significantly different from values obtained with dimaprit ($p < 0.01$).

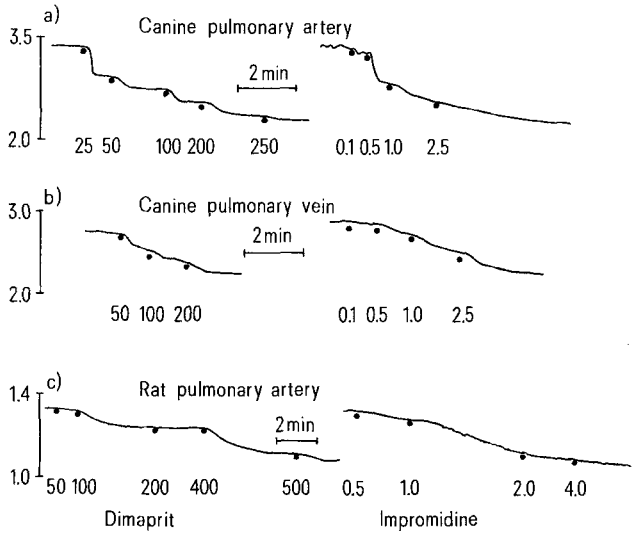

Fig. 1, a-c. Typical concentration-response (relaxant) curves of dimaprit and impromidine on norepinephrine-contracted isolated pulmonary artery and vein of dog and pulmonary artery of rat. Agonist concentrations are expressed in µg/ml of Krebs Ringer solution (added at dots). Norepinephrine was added to induce contraction in the following concentrations: canine pulmonary artery (0.1 µg/ml), canine pulmonary vein (0.5 µg/ml), and rat pulmonary artery (0.1 µg/ml). Vertical bars at left represent tensions in g. Horizontal bars represent time scales.

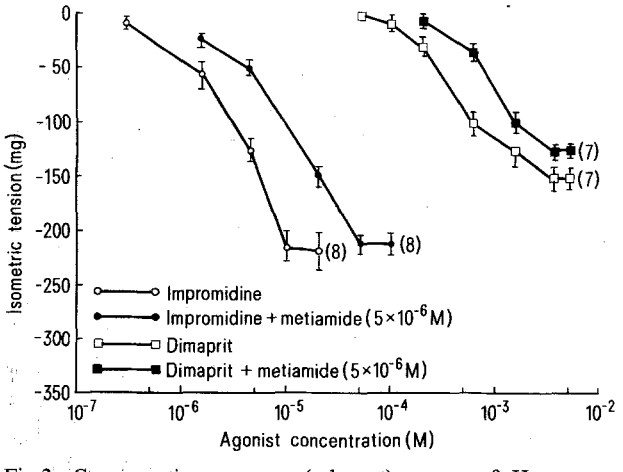

Fig. 2. Concentration-response (relaxant) curves of H_2-receptor agonists in the presence and absence of metiamide on isolated rat pulmonary arteries. O—O, impromidine alone; ●—●, impromidine + metiamide (5×10^{-6} M); □—□, dimaprit; ■—■, dimaprit + metiamide (5×10^{-6} M). Figures in parentheses denote numbers of different arteries utilized.

pyrilamine[8]. The enhancement of histamine-induced contractions on canine pulmonary arteries by metiamide (H_2-antagonist), as well as the marked relaxant responses to impromidine and dimaprit (H_2-agonists) on both canine pulmonary veins and arteries, demonstrated here, indicate the occurrence of a significant population of H_2-inhibitory receptors in isolated canine pulmonary blood vessels as well. Others have demonstrated the occurrence of H_2-inhibitory receptors in isolated pulmonary arteries of puppies[9], but the present report is the first demonstration of such receptors in pulmonary arteries and veins of adult dogs and rats.

The exposure of the rats to chronic hypoxia results in mast cell hyperplasia in the lungs[10]. Mast cells contain large amounts of histamine, which could be released during hypoxia and may produce a beneficial (pulmonary vasodilator) effect in HPV by activating H_2-receptors. This tenet is currently being investigated.

In conclusion, the occurrence of inhibitory histamine H_2-receptor's in mammalian pulmonary arteries and veins could conceivably play a modulatory (protective) role in hypoxic pulmonary vasoconstriction.

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