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# CLASSIC ARTICLE

## *Commentary by J.W. Black on*

## An analysis of the depressor responses to histamine in the cat and dog: involvement of both $H_1$ and $H_2$ receptors

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(*Br J Pharmacol* (1975), **54**, 319–324)

The qualitative part of this story was described briefly in 1972 when we reported on burimamide as a prototype histamine $H_2$-receptor antagonist. The purpose of the present paper was to produce a quantitative account of the phenomenon. The phenomenon, namely the difficulty in blocking the hypotensive effects of histamine by antihistamine drugs, was first described by Staub in 1939. Folkow, Haeger and Kahlson in 1948 confirmed the observation and suggested that other histamine receptors might be involved. When we were developing burimamide we showed that the drug was unable to block the hypotensive effects of histamine in intact animals. My recollection is that we did not look at interactions between $H_1$- and $H_2$-receptor antagonists at that stage. The surprise for me happened when we started human studies. John Wylie was one of the earliest volunteers. The interaction between burimamide and histamine-stimulated gastric acid secretion was carried out on him after an intramuscular dose of the $H_1$-receptor antagonist, mepyramine. In spite of the $H_1$-receptor blockade the subsequent i.v. infusion of histamine produced a bright red face, engorged conjunctivae and a headache. However, when the $H_2$-receptor antagonist was now infused all the vascular reactions to histamine (including a marked spreading flare around the vein being injected with histamine) gradually disappeared. I still love showing my colour slide of Wylie's face before and after, such was the impact of the observation on me.

This paper shows that $H_2$-receptor blockade has no effect on histamine-induced hypotension, that $H_1$-receptor blockade produces a small shift in the dose-response curves and that after this, $H_2$-receptor blockade can now move the dose-response curves out in parallel. We then used Ariens' two receptor model (Ariens, van Rossum & Simonis, 1959) to explain that this is the expected result where either receptor arm can produce a maximum response but the $H_2$ receptor arm is about ten fold less potent.

Another valedictory paper, this one winding up my part in the $H_2$-receptor antagonist story.

## References

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