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CLASSIC ARTICLE

Commentary by J.W. Black on

Receptors mediating some actions of histamine

A.S.F. Ash & H.O. Schild

(*Br J Pharmacol Chemother* (1966), **27** (2), 427–439)

This Commentary on a classic paper by Ash and Schild (*Br. J. Pharmacol.* 1997, **14**, 48–58) reflects James Black's fascination with receptor classification and theory. It is followed by another classic paper by Black and colleagues (*Br. J. Pharmacol.* 1975, **84**, 561–571) on the modelling of pharmacological data: this time using 5-HT rather than histamine.

Heinz Schild's fascination with the pharmacology of histamine started in 1934 when he studied (with de Burgh Daly at Edinburgh) the release of histamine during anaphylaxis. His fascination continued throughout his life. His struggles to develop a reliable bioassay for histamine led to the famous paper of 1942 in which he showed how the principles of analysis of variance, developed by Fisher to interpret agricultural experiments involving blocks of land, could be applied to bioassay involving randomised blocks of time. During a long and fruitful post-war collaboration with Jack Mongar, they studied the chemical agents and mechanisms involved in histamine release from mast cells. The importance of histamine to Schild's research career was illustrated by the title of his inaugural lecture in 1962, as Professor of Pharmacology at University College London - 'Adventures with Histamine'.

I do not known how Schild developed an interest in bioassay using gastric acid secretion as the end point. Nevertheless he assayed histamine and cholinomimetics as well as gastrin and urogastrone using the Ghosh and Schild preparation. Although he never reported on the effect or lack of effect, of antihistamine drugs on histamine-stimulated acid secretion, he was surely well aware of the phenomenon. He was also surely well aware of Trendelenberg's use of his (Schild's) pA_2 concept to attempt to classify the histamine receptors in heart muscle in which he concluded that cardiac histamine receptors differ from those found in smooth muscle (Trendelenburg, 1960). My guess is that Trendelenberg's paper triggered Schild's interest in analysing the problem using multiple bioassays and as many histamine derivatives and analogues that he could lay his hands on. Hence this paper.

I read this paper a few years ago when I was writing a biography of Heinz Schild. Revisiting it again has been enjoyable and stimulating. Table 2 shows the essence of Schild's thinking on receptor classification. Using guinea-pig ileum for the assays, the measure of pA_2 values for seven different agonists, covering a 300-fold range in activity, were not significantly different from each other. If agonists and antagonists are simply acting and interacting at the same molecular sites, then the agonists are just titrating the sites not occupied by the antagonist, so that the potency of the agonist is irrelevant in antagonist studies using the null method. That was essentially the argument in his critical paper published in 1959 with Arunlakshana. He obviously felt confident that the receptors on various smooth muscles which were blocked by mepyramine constituted a homogeneous class. Perhaps with Raymond Ahlquist's α and β receptors in mind (just a wild guess) he designated this class H_1.

The article that this commentary referred to is being republished in this supplement for the benefit of interested readers, and follows this republished commentary.

The summary of the paper reports that 'No specific antagonists were found for the actions of histamine on rat uterus and stomach. These actions are therefore unlikely to be mediated by H_1-receptors'. Unfortunately, the Results Section of the paper does not record what experiments for potential antagonists were done. I say unfortunately because the text reports that '2 mercapto histamine, when given in appropriate concentration, antagonised the effect of histamine on gastric acid secretion in the rat, but the compound was a partial agonist'. I have two regrets, I wish I had known this (with hindsight) when, a mere 25 miles away, we were trying to synthesise H_2-receptor antagonists. My other regret is that 2-mercapto histamine is a trivial name and not chemically unambiguous. In these hard-nosed days of utilitarianism in research, I suppose this problem will never be revisited. Pity!

Finally, I find it hard to accept Schild's apparent diffidence in judging that the high correlation between agonist potencies on two such different systems - stimulation of gastric acid secretion and inhibition of carbachol-stimulated contractions of the isolated rat uterus - did not have a heuristic value in terms of receptor mediation. I think that we would not be so diffident today - and probably err!

A footnote. Having initiated the notation H_1-receptor, we had to follow suit with H_2-receptor. When we gave out first presentation to a surgical society, the chairman reading the title of our paper referred to a new hydrogen receptor antagonist.

Reference

Arunlakshana, O. & Schild, H.O. (1959). Brit. J. Pharmacol. Chemother., 14, 48–58.

Trendelenburg, U. (1960). The action of histamine and 5-hydroxytryptamine on isolated mammalian atria. J. Pharm. Exp. Ther. 130, 450–460.