LETTER TO THE EDITOR

INVOLVEMENT OF H_1 - AND H_2-RECEPTORS IN TRIPLE RESPONSE TO HISTAMINE IN HUMAN VOLUNTEERS

Sir,

(Received on Jyly 21, 1984)

Histamine injected intradermally produces the characteristic 'triple response', initial redness being due to direct vasodilation, the following irregular, brighter 'flush' (flare) being due to histamine-induced axon reflexes, and the 'wheal' due to increased capillary permeability. While both H_1– and H_2–receptors have been shown to be involved in capillary dilatation and H_1–receptors alone in increased capillary permeability (6), the role of H_2–receptors is uncertain, A recent report suggesting anti-inflammatory role for H_2–antagonists (2) led us to revaluate the role of H_2–receptors in 'triple response'.

Healthy human volunteers of either sex (19-35 years of age) with no history of allergic dermatitis, asthma or other forms of allergy served as subjects. Informed written consent of all volunteers was obtained.

The front of both the forearms was cleaned with spirit and 0.02 *ml* of drug was placed in a specified order at 4 spots. Proximal and distal spots on right forearm were designated A and B, while those on left forearm were designated C and D respectively. After placing the drops in a specified order, a scratch in the form of a cross (6mm X 6mm) was made through all the drops using a sharp sterile No. 23 needle. After 1 min the areas were wiped clean. After 15 min, the areas of flare and oedema were marked using a sketch pen and immediately a graph paper was pressed against it so that imprint of the area marked was obtained on the paper and could be measured as mm_2.

In the first set of experiments (n=10), the spots A, B, C and D were painted with histamine acid phosphate, histamine + adrenaline hydrochloride, histamine + ranitidine hyrdochloride and histamine mepyramine maleate, respectively. Strength of each solution was 0.1%. In the second set of experiments the same procedure was repeated using the 0.5% sotutions of ranitidine, adrenaline and mepyramine. In the third set of experiments only spots A and C were used and were painted with a mixture of 0.1% histamine, + 0.5% ranitidine and mepyramine (spot A) and with 0.9% Nacl solution only (spot B).

In each set of experiments, results were expressed as mean (±SEM, n=10) the response being expressed as % of that caused by histamine alone. Paired 't' test was used for evaluation of differences between the groups.

Ranitidine, mepyramine and adrenaline significantly reduced the flare in a dose-dependent manner (Fig. 1). This is in agreement with Douglas (6), suggesting the role of H_1– and H_2–receptors in histamine–induced capillary dilatation.

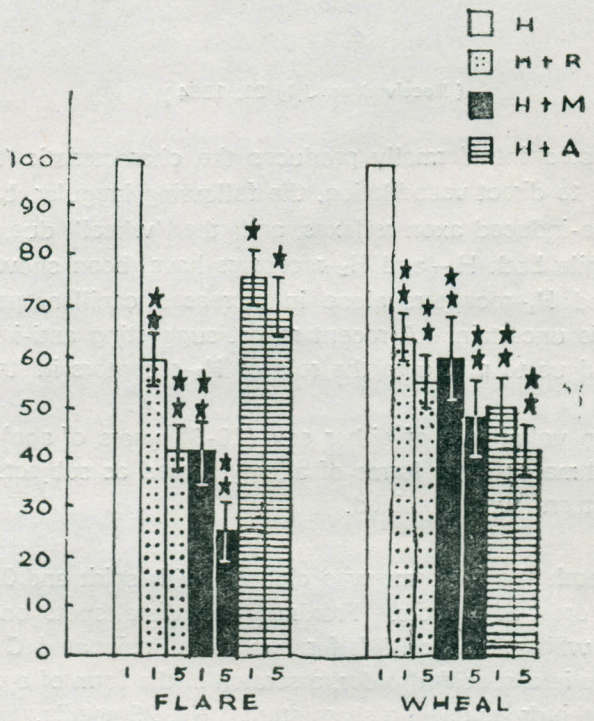

Fig. 1 : Histamine (H)–induced 'flare' and 'wheal' in human volunteers. The blocks represent mean % response (histamine=100, n=10) ± S.E.M. (vertical bars). Figures at bottom indicate strength of solutions used : R, ranitidine; M, mepyramine and A, Adrenaline, (1=1 *mg 1 ml*, 5=5 *mg/ml*). Value differs significantly from H (*P<0.01, **P<0.001, paired 't' test).

The wheal due to histamine was reduced significantly and in a dose-dependent manner by both ranitidine and mepyramine (Fig. 1). Thus, both H_1– and H_2–receptors might be involved in the regulation of capillary permeability. These findings are reminiscent of those of Joo and Csanda (7) and Brimblecombe *et al*, (4) who reported that metiamide and cimetidine suppress irradiation or thermal oedema. Other workers have reported that histamine induced increase in vascular permeability in the rabbit synovium is mediated via H_2-receptors (1). However, our findings are not in agreement with those of Douglas (6) and Bhargava *et al.*(3) that H_1-receptors alone are predominantly involved in the histamine-induced increased capillary permeability.

Adrenaline significantly decreased both the flare and wheal components of the triple response, as expected, the drug being a vasoconstrictor, acting as a 'physological antagonist.'

Combination of ranitidine and mepyramine even in higher concentrations (0,5%) failed to block completely the flare and wheal caused by histamine, and apparently other factors are involved in the manifestation of the triple response.

Youlten (8) reported that most forms of acute and chronic inflammation were not inhibited by the classicical H_1–receptor antagonists, but cimetidine was shown to be useful in rat adjuvant arthritis model (2), suggesting the role of H_2–receptors in inflammation. Our study further demonstrates a partial role of H_2–receptors in the action of histamine on capillary permeability and suggests use of H_2–antagonists in clinical inflammation, since the local action of histamine resembles the inflammatory response (5).

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