this was an indirect effect associated with erythema.

Increase in activity was consistently induced by these irritants in 17 moderate–high threshold C-mechanoreceptor units (with conduction velocities 0.3–1.0 m/s). The order of relative potency of the irritants was VAN > CAP > CR > CN > CS. CN, CR and VAN generally induced rapid tachyphylaxis and cross tachyphylaxis. When a receptor had developed tachyphylaxis to VAN, exposure to CN and CR failed to elicit activity. However when a receptor had developed tachyphylaxis to CN and CR, exposure to VAN still elicited activity. CAP seemed in this respect to be similar to VAN.

The onset of response to CR, CN and CS (5×10^{-4} M) showed a delay of 5.0–8.1 min whereas VAN was immediately (< 1.4 min) effective. When CR was applied in an alcoholic solution of 10^{-1} M, or the skin over the receptor area was broken, onset of activity was immediate. This suggests that the delay was mainly due to the permeability barrier of the skin. The average duration of action of most of these irritants was 24.3 min, though the action of CAP was briefer (approx 10 min).

The observation that these irritants affect selectively high-moderate C-mechanoreceptor units is consistent with the concept that C-fibre stimulation is associated with a sensation of dull burning pain (Landau & Bishop, 1958). Thus these chemical irritants could represent a useful tool for identifying peripheral nociceptors.

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Profiles of different anti-allergy effects of a new histamine antagonist, BM 15,100

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Several anti-allergy compounds possess multiple actions on the anaphylactic mechanism, including inhibition by H_1 histamine-receptor blocking agents of antigen-induced histamine release. This effect, was shown by Lichtenstein & Gillespie, 1975, in the isolated, sensitized human leucocyte preparation, *in vitro*, by concentrations of the order of 10^{-4} M. The high concentrations required for inhibition lead these authors to doubt the practical significance of their finding. We investigated a new histamine antagonist, BM 15,100:3,4-dimethyl-7-[4-(*p*-chlorobenzyl)-piperazin-1-yl]-propoxycoumarin. dihydrochloride, (Boehringer Mannheim), assessing its antagonism to histamine and other agonists. Its ability to inhibit anaphylactic histamine release in the human leucocyte test model was also investigated. Histamine release was measured by a spectrofluorometric technique.

We found BM 15,100 to be a potent antagonist of histamine in guinea-pig ileum, with a pA_2 of 9.8, after 3 min pre-incubation with antagonist, and in guinea-pig spiral tracheal strips.

Concentrations exceeding 10^{-6} M lead to irreversible antagonism and lack of recovery, which could not be averted by increasing the agonist concentration. BM 15,100 also showed relatively weak antagonism of slow reacting substance of anaphylaxis, 5-hydroxytryptamine, prostaglandins E_1, E_2 and $F_{2\alpha}$, bradykinin, and angiotensin in isolated guinea-pig ileum, with pA_2 values ranging from 5.6 to 6.1 for all of these agonists. The compound also antagonized PGE(s), $PGF_{2\alpha}$, and angiotensin in rat uterus, with pA_2 values of similar order. This compound also inhibited antigen-induced histamine release from sensitized human leucocytes, but the dose-response curve exhibited a point of inflexion. Thus, small inhibition was seen with 10^{-7} M which increased to a maximum of 75 to 100% with concentrations ranging from 10^{-6} to 10^{-5} M, but further increase to 10^{-4} M

not only reduced the inhibition, but occasionally produced histamine release by itself.

Another effect that this compound possessed was its ability to inhibit the uptake of labelled histamine by isolated human leucocytes, in a dose-dependent fashion. This is a property of histamine antagonists, recently reported by one of us (Assem, 1976).

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Anti-allergic properties of a new coumarin compound (BM 15,100)

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BM 15,100, a compound chemically defined as 1-(4-Chlorobenzyl)-4 3-(3,4-dimethylcoumarin-7-yl-oxy)-propyl -piperazine dihydrochloride combines two types of pharmacological activity useful for medical therapy of anaphylactic diseases such as atopic asthma and hay fever: (1) inhibition of mediator release from tissue mast cells and (2) antagonism to the effect of mediators.

The passive cutaneous anaphylactic (PCA) reaction in rats mediated by reaginic antibodies (Goose & Blair, 1969) was significantly inhibited by BM 15,100 (0.75 mg/kg i.v.). The same dose of this compound significantly suppressed degranulation of mesenteric mast cells (MD) (Fügner, 1973) and the cutaneous reaction elicited by intradermal injection of histamine. The PCA- and MD-inhibitory activity of BM 15,100 was similar to that of disodium cromoglycate (DSCG). Mepyramine antagonized PCA at a dose of 3 mg/kg i.v. whereas 0.38 mg/kg i.v. were sufficient to inhibit the histamine reaction. These results suggest that the PCA inhibition by BM 15,100 observed in our experiments was caused mainly by suppression of MD and only partly by the antihistamine activity. In contrast to the lack of activity of DSCG on oral administration, oral doses of BM 15,100 inhibit PCA in the rat significantly at doses nearly identical with the corresponding intravenous doses.

The oral antianaphylactic activity was also demonstrated in experiments with guinea pigs. Conjunctival oedema and hyperaemia in anaphylactic conjunctivitis (Dwyer, Turk & Darougar, 1974) were inhibited significantly by BM 15,100 at a dose of 0.75 mg/kg, anaphylactic bronchospasm (Davies & Johnston, 1971) was suppressed significantly with 0.4 mg/kg orally.

The naturally occurring allergy of monkeys to ascaris-antigen can be considered as a reliable *in vivo* model of human reagin mediated anaphylaxis. Active cutaneous anaphylactic (ACA) reactions were evoked in stump tail monkeys by intradermal injections of different dilutions of ascaris antigen (Perper, Sanda & Lichtenstein, 1972), and one cutaneous reaction in every experiment by intradermal injection of histamine. We measured the skin reaction by multiplying the diameter of the wheal by an arbitrary score for colour intensity. BM 15,100 in a dose as low as 0.1 mg/kg, given orally, significantly and strongly inhibited ACA whereas the histamine reaction was suppressed to a lesser degree. With doses up to 0.8 mg/kg there was no further increase in ACA inhibition but a clear dose-response relationship for the histamine antagonism could be seen. This finding is in agreement with the above-mentioned result from the intravenous injection into rats in so far as the histamine antagonism does not seem to be decisive for the inhibition of the anaphylactic reaction by BM 15,100.

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