

Experimental Pruritus Evoked by Platelet Activating Factor (PAF-Acether) in Human Skin

BO FJELLNER and ÖSTEN HÄGERMARK

Department of Dermatology, Karolinska Hospital, Stockholm, Sweden

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Cutaneous pruritic effects of synthetic platelet activating factor (PAF-acether) and, in particular, its interference with dermal mast cells, were studied in human volunteers. Intradermal injections of 10-100 ng produced dose-dependent flare and itching responses. The cutaneous reactions were inhibited by local administration of the H₁ antihistamine mepyramin. The cutaneous responses were also markedly reduced in histamine-depleted skin. These findings indicate that the cutaneous responses produced by PAF-acether were mediated via an indirect and mainly histamine-dependent mechanism. *Key words: Pruritus; Platelet activating factor (PAF-acether).* (Received January 15, 1985.)

B. Fjellner, Department of Dermatology, Karolinska Hospital, S-10401 Stockholm, Sweden.

Inflammatory processes eliciting itch are likely to involve the dermo-epidermal junction area (1). The responsible biochemical events are, however, incompletely studied (2, 3). Several inflammatory agents have been considered as mediators of pruritus, such as biogenic amines, polypeptides, proteolytic enzymes and lipids. PAF-acether may also be a pruritogenic mediator, as it is a recently described biologically active lipid that is released from several inflammatory cells with properties appropriate to those of a mediator of inflammation (4). The aim of this study was to observe the pruritic effects evoked by intradermally injected PAF-acether. Since most inflammatory agents with pruritogenic effects seem to act indirectly via release of histamine from dermal mast cells (5, 6), we also evaluated this possibility by observing interference of an H₁-antagonist or a histamine depletion procedure on the cutaneous responses evoked by PAF-acether in human skin.

MATERIAL AND METHODS

Fifteen healthy volunteers, one male and 14 females, aged 20 to 50 years (median age 28 years), took part in this study. None of the subjects was of an atopic constitution. All oral and topical drugs were prohibited for one week prior to the test procedure. Cutaneous reactions were produced on the lateral aspects of the upper arms by intradermal injection of 0.01 ml of histamine hydrochloride (ACO AB, Solna, Sweden), 10 µg/ml; the histamine liberating agent compound 48/80 (LEO AB, Helsingborg, Sweden), 10 µg/ml; and PAF-acether (Calbiochem, San Diego, Ca, USA), 1-10 µg/ml. The structure of PAF-acether is illustrated in Fig. 1. All substances were dissolved in sterile pyrogen-free physiological saline containing 10% (v/v) Sörensen phosphate buffer (Na₂HPO₄+KH₂PO₄, 67 mM), pH 7.4. Itch duration was recorded. Axon-reflex mediated flare reaction was outlined on the skin with a marking pen 5 min after injection and traced onto a transparent plastic film where the area was measured with a planimeter (model 317 from Gebrüder Haff BmbH, Pfronten, W. Germany). Reproducibility of this technique, expressed as coefficients of variation (mean values), is 13% for histamine-evoked itch and 7% for flare, while the corresponding figure for compound 48/80 elicited itch is 18% and for flare 12% (2). Histamine depletion of dermal mast cells was obtained by intradermal injection of 0.1 ml of compound 48/80, 100 µg/ml, in a mixture with mepyramin, 100 µg/ml, in order to minimize the immediate effects of histamine when released. The injections were repeated at three identical spots once a day for 3 consecutive days, followed by the test procedure on the fourth day. Saline combined with mepyramin in identical volumes and concentrations was used at control sites. The experimental design was performed in a single blind procedure.

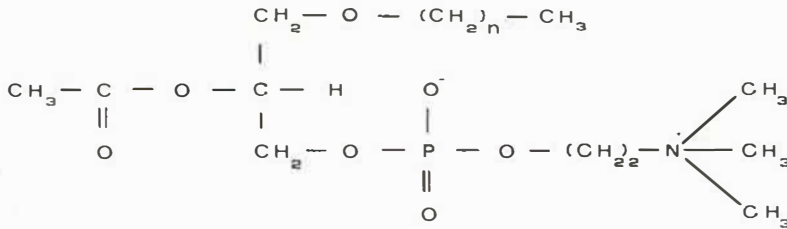


Fig. 1. Structure of platelet activating factor (PAF-acether).

Statistical method

The results were statistically analyzed with Student's *t*-test for paired samples.

RESULTS

The results are presented in Figs. 2 and 3. PAF-acether produced dose-response related flare and itch reactions when injected intradermally. Three of eight subjects reported itch after the lowest dose of PAF-acether (10 ng), whereas all volunteers recognized pruritus after the two higher doses (33 and 100 ng). A concomitant wheal response was also observed but not quantified. Production of any late responses was not investigated. The H₁ antihistamine mepyramin inhibited the cutaneous responses about as effectively as those produced by histamine ($p < 0.01$, itch and $p < 0.001$, flare). The reactions evoked by PAF-acether in histamine-depleted skin were markedly reduced when compared with those in control sites ($p < 0.05$, itch and $p < 0.001$, flare). The same response pattern was observed for the histamine liberator compound 48/80 ($p < 0.01$, itch and $p < 0.001$, flare), whereas histamine *per se* elicited responses of similar magnitude in histamine-depleted and control skin.

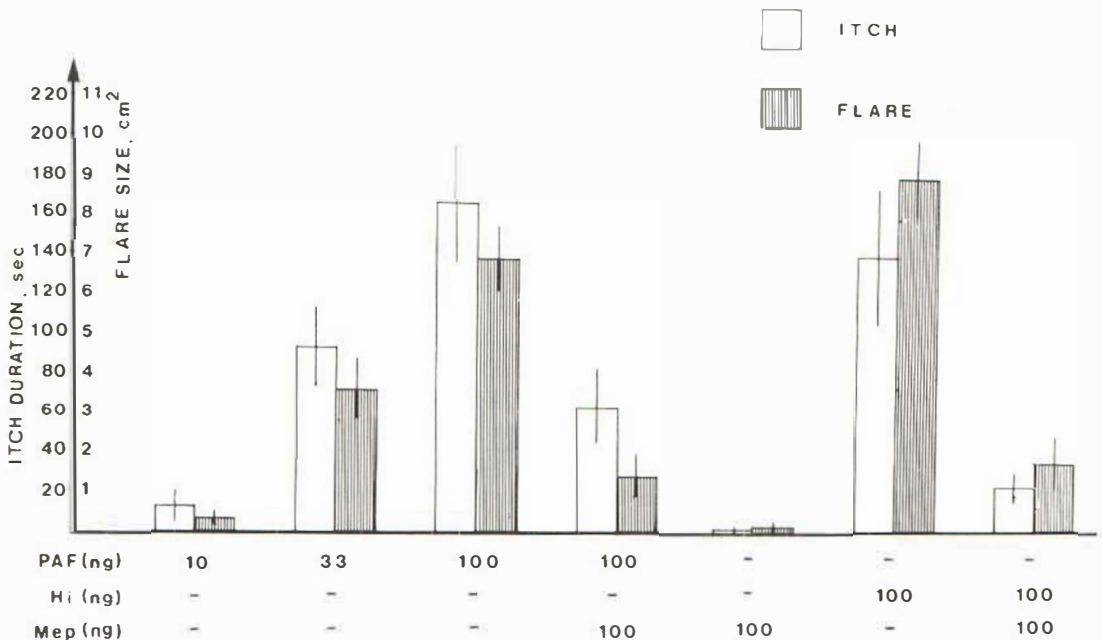


Fig. 2. Itch and flare responses evoked by intradermal injection, 0.01 ml, of PAF-acether (PAF), histamine (Hi), mepyramin (Mep) and a mixture of mepyramin with either PAF-acether or histamine (mean \pm SE; $n=8$).

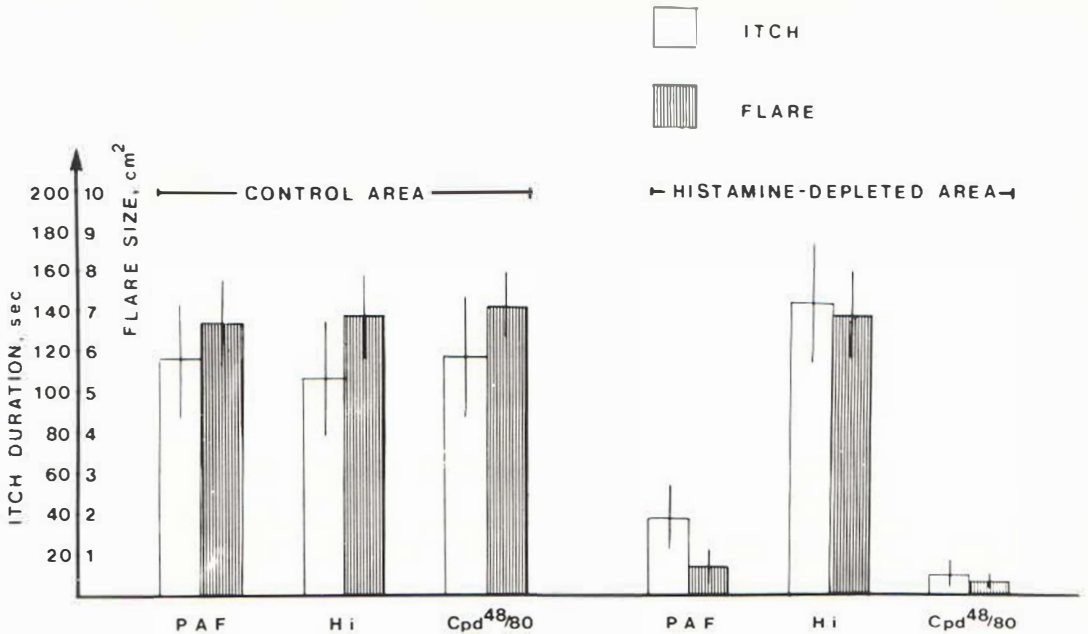


Fig. 3. Influence of histamine depletion on itch and flare responses induced by intradermal injection, 0.01 ml, of 100 ng of PAF-acether (PAF), histamine (Hi) and compound 48/80 (mean \pm SE; $n=9$).

DISCUSSION

Research in the early 1970's on inflammatory mediators and their biological effects disclosed a leucocyte-dependent degranulation of platelets in rabbits (7). The responsible potent factor (1-*o*-alkyl-2-acetyl-sn-glycerol-3-phosphorylcholine) was referred to as platelet activating factor (PAF-acether) (8) or AGEPC (9). PAF-acether constituted a new family of ether-linked phospholipids not belonging to the arachidonic acid cascade, such as leukotrienes, prostaglandins, thromboxanes and related substances. It is produced by a number of inflammatory cell types (10). It has platelet-dependent biological effects, unaffected by, for example, cyclooxygenase inhibitors such as aspirin (10), and platelet independent effects (for ref see 4). The effects seem to be specific, since lyso-PAF, although it has similar physicochemical properties (10), is biologically inactive (11). The biological effects are appropriate to those of an inflammatory mediator. PAF-acether may thus be involved in inflammatory, pruritic and other pathological processes.

PAF-acether injected intradermally in human skin produces a biphasic inflammatory response with an early dose-related wheal and flare reaction and a succeeding late-onset erythema (11, 12, 13), as well as a histological inflammatory cellular infiltration (14). The mechanisms producing the increased vascular permeability, axon reflex vasodilation and pruritic response are not fully determined. The plasma protein extravasation, however, seems to be mast cell independent, at least in animals, since it is not significantly attenuated by mepyramin (12, 15). The role of endogenous histamine release in the pruritic and axon reflex reactions is unknown.

Itching has not been mentioned in the hitherto reported investigations of the cutaneous effects of PAF-acether. One factor for this omission may be that too large volumes have been utilized. It was already pointed out in the 50's by Shelley & Arthur that this is a critical factor, probably due to a pressure effect blocking the pruritic response (1).

The present results indicate that PAF-acether produces itch in human skin by release of mast cell bound histamine in dermis. Thus, previous depletion of skin histamine by treatment with the histamine liberator compound 48/80 effectively reduced the cutaneous itch and flare responses induced by PAF-acether. Moreover, antihistamine also locally diminished the PAF-acether produced reactions. An indirect effect of PAF-acether produced reactions via histamine release from dermal mast cells therefore seems likely. The question of whether platelet activating factor has a physiological and pathological role in itching states is therefore tentative, but unproved, in spite of its potential.

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