Platelet-Activating Factor-Induced Immediate and Late Cutaneous Reactions

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Abstract

In atopic subjects, intradermal injection of platelet-activating factor (PAF), 40 and 400 ng, resulted in an immediate edema reaction markedly blocked by cetirizine, 10 mg twice a day. PAF challenge also induced a significant eosinophil accumulation evidenced by a skin window technique at 2, 4, 8 and 24 h. This inflammatory phenomenon was significantly inhibited by cetirizine. In patients with chronic urticaria, PAF, 100 µg intradermally, induced immediate and late cutaneous reactions (LCR) also blocked by cetirizine, 10 mg twice a day. These LCR were accompanied by an infiltration of the deep dermis by degranulated eosinophils. The pathophysiological mechanism of the PAF-induced skin reactions is discussed as well as the mechanism of action of cetirizine.

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The increased vascular permeability induced by intradermal injection of platelet-activating factor (PAF) has been described by several investigators in experimental animals as well as in humans [1–4]. According to these authors, the PAF-induced flare is easily blocked by previous administration of H₁ antihistamines while the wheal appears rather poorly H₁-dependent. This is in accordance with the fact that PAF does not act as a histamine releaser in isolated human skin mast cells in vitro [5].

Nevertheless, we recently performed two clinical pharmacological studies in skin of atopic patients and patients with chronic urticaria challenged with PAF (40 and 400 ng in the atopies and 100 µg in the urticaria patients), and we showed that pretreatment with cetirizine, 10 mg twice a day (a dose which completely abolishes a skin wheal induced by a prick histamine at 500 mg/ml), not only inhibited the development of the flare but also markedly inhibited the wheal formation (50% decrease) [6,7].

Moreover, PAF, 100 µg intradermally, induced the development of a typical endematous and erythema-tous late cutaneous reaction (LCR) in urticaria patients, a phenomenon that was inhibited by 80% by cetirizine pretreatment.

Taking into account all these above-mentioned data together with the facts that PAF was shown to in-

duce a nonimmunological release of leukotrienes [8] and that a PAF-induced skin reaction may be blocked by PAF antagonists [9–11], it becomes possible to propose the following hypothetical mechanism in order to explain the immediate PAF-induced skin reaction in humans.

The flare might result from a classical axon reflex phenomenon mediated by PAF receptors on the nerves' endings of the C fibers. As far as the wheal is concerned, we might assume that it partly depends on a direct effect of PAF on the skin vessels on the one hand, and on the other hand that it is partly due to a local appearance of other vasoactive mediators such as leukotrienes and histamine. The origin of these mediators remains to be determined. A local interference

between these vasoactive mediators (PAF, leukotrienes, histamine) and neuromediators released locally cannot be excluded.

The PAF-induced LCR observed in urticaria patients may be partly secondary to the local increase in vessel permeability allowing plasma factors to infiltrate the perivascular spaces and to cause a local delayed inflammation. Indeed, it must be emphasized that the intradermal injection of the urticaria patient's own serum is followed by an LCR peaking at 6 h. If histamine represents a significant part of the mediators responsible for the observed increase in vessel

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permeability, this may explain the marked inhibiting effect of cetirizine on this LCR. Nevertheless, the serum-induced LCR is rather small in comparison with the LCR induced by PAF, and this is why a second possibility for explaining the PAF-induced LCR is the marked infiltration of the deep dermis by de-granulated eosinophils [12]. Actually, the PAF-induced LCR in urticaria patients might be due to a conjunction of vessel hyperpermeability and eosinophilic infiltration.

Similarly, the inhibiting effect of cetirizine on this LCR might also be linked to the well-documented inhibition by cetirizine of the eosinophils' migration [13–17].

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