SHORT REPORTS

Tetracycline Does Not Affect the Trauma- and Leukotriene B4-induced Intraepidermal Accumulation of Polymorphonuclear Leukocytes

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The transepidermal migration of polymorphonuclear leukocytes is a well established target for antipsoriatic therapies. Tetracycline, although inhibiting the movement of PMN, is not an effective treatment for psoriasis. In contrast to the inhibition of PMN chemotactic response to serum and bacterial products, the leukotriene B4-induced and trauma-induced intraepidermal accumulation of PMN was unaffected by tetracycline.

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The intraepidermal accumulation of polymorphonuclear leukocytes (PMN) is one of the earliest and perhaps most characteristic constituents of the psoriatic lesion (1). In order to study the interference of drugs with the dynamics of this process 2 experimental models are available. The intraepidermal accumulation of PMN following sellotape stripping is the response to a standardized endogenous release of mediators of inflammation (2). The intraepidermal accumulation of PMN following epicutaneous application of leukotriene B4 (LTB4) is another reproducible model, in which a standardized exogeneous stimulus is given (3, 4). Eretinate, acitretin, methotrexate, phototherapy, photochemotherapy, dithranol and topical corticosteroids—although strikingly different therapeutic approaches—share 2 characteristics: a well established antipsoriatic effect clinically and a profound inhibition of intraepidermal accumulation of PMN in these models (4–10).

Tetracyclines have been reported to interfere with PMN functions in vitro and in vivo (11–14). Surprisingly, these drugs are not part of the repertoire of antipsoriatic therapies. However, as far as we know, the LTB4-induced PMN accumulation has never been reported to be inhibited by tetracyclines. In the present investigation the interference of an oral course of tetracycline with the trauma- and LTB4-induced intraepidermal accumulation of PMN was studied.

MATERIALS AND METHODS

Nine subjects without signs or previous history of skin diseases participated in the study. The group consisted of 2 females and 7 males, aged between 22 and 35 years. No subject had received any medication for at least 3 months prior to the study. Prior consent of the medical ethics committee was obtained for these experiments. The volunteers received an oral course of tetracycline in doses of 250 mg four times a day for 10 consecutive days. One day before initiation of the therapy, and on the 3rd and 10th day of the treatment, LTB4 was applied and sellotape stripping was carried out.

LTB4 was purchased from Pascel GmbH Frankfurt, Germany. Aliquots of 10 ng LTB4 in ethanol were applied in 10 μl droplets through glass cylinders (diameter 5.5 mm) on the upper back skin and ethanol was evaporated under a stream of nitrogen (3, 4). Application sites were marked with eosin and covered with impermeable dressings (Silverpatch, Van der Bend, Brielle, The Netherlands). At the same time circular areas (diameter 15 mm) were stripped on areas at least 10 cm from the LTB4 sites by repeated applications of sellotape. Removal of the stratum corneum was considered complete when the whole area appeared to be glistening (30–40 applications). Biopsies were taken from the stripped areas and from the LTB4-treated sites 8 h and 24 h after these challenges, respectively. No anaesthetic agent was employed. All specimens were cut fresh, using a razorblade in conjunction with a metal guard. The biopsies (fresh weight 2–3 mg, approximately 3 mm diameter and 0.2 mm thick) were processed for elastase measurement.

Analytical procedures were as described previously (2, 15). In brief, the biopsies were rinsed thoroughly in phosphate buffered saline, homogenized in buffer containing cetromide and centrifuged. Elastase activity of the supernatant was determined by measuring the fluorescence of 4-methyl-7-aminocoumarin, released from the substrate MeOSuc-Ala-Ala-Pro-Val-N-methylcoumarin. Endogenous inhibition was corrected for by the inclusion of an internal standard of elastase (equivalent to 500 PMN). The density of infiltrating PMN per 10 μg skin was calculated using the value of 0.66 pmol 4-methyl-7-aminocoumarin released per hour per PMN (2).

Statistical evaluation was performed using the Wilcoxon rank test for paired samples.

RESULTS

Tetracycline in dosages of 1 g a day were well tolerated by all the subjects. Only one of them had experienced a mild gastrointestinal discomfort on days 9 and 10 of the treatment period.

PMN accumulations 8 h following sellotape strip-
Fig. 1. Accumulation of PMN, induced by seborrheic stripping at different time intervals before and during treatment with tetracycline. Bars represent mean ± SEM.

Fig. 2. LTB4-induced accumulation of PMN before and during treatment with tetracycline. Bars represent mean ± SEM.

ping and 24 h following the application of LTB4 before and during treatment with tetracycline are shown in Figs. 1 and 2. Both trauma- and LTB4-induced PMN accumulations were unaffected by tetracycline (p > 0.05). The percentage inhibition of a standard preparation of elastase by all the skin biopsies examined was 13 ± 1.5% (mean ± SEM) and no statistically significant difference could be shown from the inhibitory activity of 12 ± 4.0% reported for normal unchallenged skin (15) (p > 0.05).

DISCUSSION

The present investigation clearly shows that an oral course of tetracycline in a dosage of 1 g a day does not inhibit the trauma- or LTB4-induced intraepidermal accumulation of PMN.

The chemotactic response of PMN to human serum, C3a, bacterial endotoxins and A3 influenza virus has been shown to be inhibited by tetracycline (11–14). To the best of our knowledge, no data are available in the literature regarding a possible interference of this drug with the chemotactic response of PMN to inflammatory eicosanoids.

The molecular basis of the interference of tetracycline with PMN chemotaxis is not clear. It has been suggested that the interference is not at the level of the PMN themselves but comprises an inhibition of the generation of chemotactic factors and binding to chemoattractants (11). However, a more recent study indicates that a direct interference with the PMN movement occurs as well (13).

In contrast to the observations in the present study tetracycline has been reported to inhibit the potassium iodide-induced intrafollicular micropustule formation (16). An explanation of this discrepancy might be a different bioavailability in these models. Tetracyclines have been reported to occur in relatively high concentrations in the follicular epithelium (17). However, using skin chambers with serum complement and bacterial culture supernatants as chemoattractants, tetracycline inhibited the PMN chemotaxis (18). Combining the present study with these observations using skin chambers it seems feasible that tetracycline does not affect the chemotactic response of the whole repertoire of chemoattractants.

A selective interference of tetracycline with PMN chemotaxis is in line with the available data on the
role of PMN as a target for antipsoriatic therapies. Although some authors suggest an effect of tetracycline in psoriatic skin (19, 20) this drug has by no means an established reputation as treatment for this disease. The negative effect of tetracycline on the LTB₄ and trauma-induced PMN accumulation is compatible with the essentially negative clinical results of tetracycline in psoriasis.

REFERENCES