The anti-inflammatory mechanisms of minocycline, an antibiotic used in the treatment of the inflammatory component of acne, are only partially understood. In addition to inflammation due to cytokines (IL-1, IL-6, TNF-α, etc.), recent studies have shown that neuropeptide-mediated neurogenic inflammation may play an important role in cutaneous inflammation. The purpose of this study was to investigate minocycline-induced modulation of cutaneous production of alpha-melanocyte-stimulating hormone (α-MSH), a neuropeptide with known anti-inflammatory activity. Two different skin models were used: explants of inflammatory skin and reconstituted skin, both incubated with minocycline at different concentrations and for different time periods. Epidermal production of α-MSH, as evaluated by immunofluorescence and immunoperoxidase techniques, showed increased expression in both models. This neuropeptide, which has an anti-inflammatory activity (notably through production of IL-10, antagonism of IL-1 and inhibition of the chemotaxis of polymorphonuclear leukocytes), thus plays a role in the anti-inflammatory action of minocycline. Key words: inflammation; α-MSH; cyclines.

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Table I. Modulation by minocycline of the expression of α-MSH by keratinocytes on reconstituted skin after 3 and 6 h of incubation with different concentrations of minocycline.

The results represent the mean of 3 experiments. Intensity of labeling: + very low intensity; ++ low intensity; +++ moderate intensity

<table>
<thead>
<tr>
<th>Minocycline (μg/ml)</th>
<th>3 h</th>
<th>6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1.5</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>3</td>
<td>+/+</td>
<td>++</td>
</tr>
<tr>
<td>6</td>
<td>+/+</td>
<td>++</td>
</tr>
<tr>
<td>10</td>
<td>+/+</td>
<td>++</td>
</tr>
<tr>
<td>100</td>
<td>+/+</td>
<td>+++</td>
</tr>
<tr>
<td>1000</td>
<td>+/++</td>
<td>+++</td>
</tr>
</tbody>
</table>

In the presence of minocycline, an increase in keratinocyte staining of α-MSH over baseline values was noted for all time periods studied, from 3 μg/ml at 3 h and from 1.5 μg/ml at 6 h. Intensity was maximal for minocycline concentrations of 100 and 1,000 μg/ml at 6 h.

DISCUSSION

This in vitro study shows that α-MSH production increased in both inflammatory and reconstituted skin beginning with the lowest minocycline concentrations tested (3 μg/ml). α-MSH is a 13 amino acid neuropeptide derived from proopiomelanocortin (POMC) (11). In skin, POMC-derived peptides are detected in C fibres (12) as well as in various types of cells: peripheral blood mononucleate cells, immune cells and skin cells (keratinocytes, melanocytes, sebocytes, Merkel cells) (13). Weak epidermal staining was found at basal state in inflammatory and reconstituted skin, which is concordant with the results of previous studies showing a lack of α-MSH keratinocyte production in the absence of stimulation (14). Epidermal staining was increased in the presence of minocycline in both inflammatory and reconstituted skin at all incubation times studied. The skin explant model allowed us to evaluate global α-MSH production in skin, whereas the reconstituted skin model provided more specific assessment of keratinocyte production. In this study, skin biopsies of psoriasis were used as inflammatory skin model, however the results obtained on the modulation of α-MSH production by minocycline may be relevant in acne where minocycline is often used. In both models, the dose-dependent increase was maximal at the highest minocycline concentrations tested, respectively 1000 μg/ml for explant model and 6 μg/ml for reconstituted skin model. These doses are higher than the mean concentrations of minocycline noted in serum (0.7–6.5 μg/ml) (9) for explant skin model, but are similar for reconstituted skin. Increased α-MSH production in the presence of minocycline could affect the different activities of the antibiotic. First, it could play a role in the anti-inflammatory activity of minocycline, since α-MSH has both a central and peripheral anti-inflammatory effect. Its central effect is apparently dependent on a modulation of the release of substance P, a neuropeptide with pro-inflammatory activity (15), and its peripheral effect on inhibition of the release of certain pro-inflammatory cytokines (IL-1, IL-6, TNF-α) (16), production of interferon-gamma (17) and
chemotaxis of polymorphonuclear leukocytes (18). Moreover, it stimulates the production of IL-10, an anti-inflammatory cytokine (19). Thus, α-MSH could contribute to the anti-inflammatory effects of minocycline by a mechanism of release from the nerve fibres containing it and subsequent synthesis by keratinocytes. In this way, it could limit the cytokine cascade, which sustains inflammatory reaction. Moreover, the increase in α-MSH production could affect the pigmentation phenomena relative to minocycline, which are rather common with this antibiotic since α-MSH stimulates melanogenesis (20). It may be concluded from this study that minocycline induces keratinocytic production of α-MSH in in vitro models, which is an additional demonstration of the anti-inflammatory properties of this antibiotic.

REFERENCES