Effects of extracellular calcium and 1,25-dihydroxyvitamin D3 on seborrhea and acne

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Introduction

Calcium (Ca2+) and 1,25-dihydroxyvitamin D3 (1,25(OH)2D3) are well-known promoters of epithelial cell functions; however no research on serum levels of Ca2+ in acne has been performed [1], despite the fact that, in several studies, treatment of acne with isotretinoin has been shown to modify circulating 1,25(OH)2D3 and Ca2+ levels [2-5]. Therefore, we evaluated extracellular Ca2+ (ecCa2+) and 1,25(OH)2D3 effects on human SZ95 sebocytes. In addition, we assessed ionized calcium and 1,25(OH)2D3 levels in acne patients and investigated the clinical relevance of the in vitro results.

Materials and methods

Experimental study: Morphology, ultrastructure, proliferation, lipid synthesis and apoptosis of SZ95 sebocytes were assessed in vitro under different concentrations of extracellular Ca2+ (ecCa2+; 0.05-1.4 mM) with or without 1,25(OH)2D3 (10-7 and 10-8 M) at 24 and 72 h in culture.

Clinical study: Serum Ca2+ and 1,25(OH)2D3 levels were assessed in 104 patients with acne [47 female and 57 male; 53% under the age of 25 years; with mild (n=81), moderate (n=22) and severe (n=1) disease] and 112 matched controls by commercial assays.

Results

SZ95 sebocytes [6] maintained at low ecCa2+ (0.05 mM) exhibited a rounded morphology, formed few loose colonies and tended to detach from culture plates (Fig. 1). Numerous mitochondria, highly developed Golgi complex and several small to large lipid droplets consistent with active cell metabolism and lipogenesis [7] were observed (Fig. 2). In contrast, SZ95 sebocytes maintained at high ecCa2+ (1.4 mM) were polygonal, readily expanded and formed large compact colonies firmly adherent to culture plates, whereas lipid droplets were barely detected. Increasing ecCa2+ levels significantly enhanced SZ95 sebocyte numbers and reduced lipogenesis (Figs. 3, 4). The intracellular Ca2+-dependent transmembrane glycoprotein E-cadherin was ubiquitously expressed in SZ95 sebocytes independently of the ecCa2+ levels at 24 h, whereas the cells expressed minor increase in E-cadherin levels at 72 h under high ecCa2+ (Fig. 5). However, its intercellular immunofluorescence signal was only present in subconfluent SZ95 sebocyte cultures under high ecCa2+ levels and was almost lost in the few attached cells under low ecCa2+ levels. Reducing ecCa2+ enhanced SZ95 sebocyte caspase 3/7 activity (apoptosis) and Ca2+ chelation by EGTA resulted in enhanced lipogenesis (Figs. 6, 7). 1,25(OH)2D3 decreased sebaceous lipogenesis as shown by functional / ultrastructure studies (Figs. 8, 9). The latter also detected signs of autophagy in 1,25(OH)2D3-treated sebocytes.

In the clinical study (Table 1), patients and controls exhibited normal serum calcium levels, whereas younger acne patients presented higher levels than older patients and controls. 81% of the acne patients presented at least 1,25(OH)2D3 insufficiency, whereas 47% of the patients were even deficient. In addition, younger acne patients presented lower 1,25(OH)2D3 levels than did older ones [Yates’ p<0.01].

Table 1. Demographic and clinical data for the patients with acne and controls.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Acne</th>
<th>Acne severity</th>
<th>Acne status</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-25</td>
<td>45</td>
<td>55</td>
<td>100</td>
<td>mild</td>
</tr>
<tr>
<td>26-35</td>
<td>30</td>
<td>70</td>
<td>100</td>
<td>moderate</td>
</tr>
<tr>
<td>36-45</td>
<td>20</td>
<td>80</td>
<td>100</td>
<td>severe</td>
</tr>
</tbody>
</table>

Conclusion

SZ95 sebocytes express the vitamin D receptor at mRNA and protein levels and possess all enzymes required for the synthesis and metabolism of 1,25(OH)2D3, the biologically active metabolite of vitamin D [8]. An anti-inflammatory effect of 1,25(OH)2D3 on human sebocytes has been shown, as 1,25(OH)2D3 reduced interleukin-1β (IL-1β) and IL-6 as well as metalloproteinase-9 expression and secretion [8, 9] at ecCa2+ levels of 0.4 mM [10]. In this study, ecCa2+ and 1,25(OH)2D3 were found to regulate sebocyte morphology, increase cell numbers and decrease sebaceous lipogenesis in vitro. They also exhibited an autophagy/lysophagy effect on SZ95 sebocytes induced by 1,25(OH)2D3 and by an ecCa2+-controlled, previously not reported, endogenously active channel mechanism [11]. Both agents, but mostly 1,25(OH)2D3 levels, may affect sebaceous lipogenesis in vivo. The increased ionized calcium as well as the reduced 1,25(OH)2D3 levels detected in the serum of younger patients with acne may contribute to the increased sebaceous gland volume and the seborrhea, which are characteristic acne signs.

References