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Tyrosine levels regulate the melanogenic response to alpha-melanocyte-stimulating hormone in human melanocytes: implications for pigmentation and proliferation.

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Source

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Abstract

Melanocyte-stimulating hormone (alpha-MSH) increases cytosolic levels of cAMP as well as tyrosinase activity in murine melanocytes. These activities depend upon the presence of melanin precursors and may differ in human melanocytes. In this study, we demonstrate that high levels of tyrosine (3.7 mM), the chief melanin precursor, reduced the proliferative effect of alpha-MSH and altered human melanocyte morphology as compared to treatment with low (25-30 microM, half-physiological) levels of tyrosine. The anti-proliferative effect of high levels of tyrosine was not restricted to alpha-MSH; tyrosine also reduced proliferation induced by forskolin, a direct activator of the cAMP pathway. Exposure to low tyrosine levels and alpha-MSH induced a dendritic morphology; in the presence of high tyrosine and alpha-MSH, melanocytes displayed large, pigmented cell bodies and less dendricity. Exposure to alpha-MSH in the presence of low tyrosine for up to 9 days did not appreciably increase melanin levels, but culturing the human melanocytes in high levels of tyrosine with alpha-MSH increased melanin levels 10-50-fold, depending on the pigmentation background of the donor. A greater induction of melanin accumulation was observed in melanocytes derived from light-skinned donors than was observed in cells obtained from dark-skinned donors. The poor ability of alpha-MSH to stimulate melanin synthesis was not caused by a lack of induction of melanogenic proteins, as alpha-MSH increased the expression of microphthalmia (MITF), tyrosinase, dopachrome tautomerase (DCT), and Pmel-17, compared to untreated cells or cells stimulated by phorbol ester alone, regardless of tyrosine levels. DCT levels were greatly induced by low tyrosine with alpha-MSH, but were dramatically decreased by high tyrosine with alpha-MSH. Interestingly, in this same medium (high tyrosine), MITF levels also decreased after 2 weeks and were barely detectable by the third week. Despite the absence of MITF at 3 weeks of treatment in high tyrosine medium, tyrosinase levels remained high, thereby suggesting that additional factors must be responsible for tyrosinase transcription in human melanocytes. Our results indicate that tyrosine levels can regulate the proliferative activity induced by alpha-MSH, as well as the extent of melanogenesis in normal human melanocytes. The significance of this work is that tyrosine levels may be part of the mechanism that switches melanocytes out of a proliferative status and into a melanin-synthesizing, terminally differentiated phenotype.

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