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Targeting the melanocortin 1 receptor for modulating skin pigmentation by agonists that stimulate sunless tanning or antagonists to treat hyperpigmentation

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Statement of the problem: In eastern cultures, white skin with no blemishes is a sign of beauty, while in western cultures tanning is desirable and desirable and associated with wellness. The melanocortin 1 receptor expressed on pigment cells, the highly desirable. Accordingly, there is a large marker for "whitening agents" as well as "tanning agents". The melanocortin 1 receptor (MC1R) expressed on melanocytes is a major regulator of constitutive skin pigmentation and the tanning response to UV. The MC1R agonist α-melanocyte stimulating hormone (α-MSH) stimulates the synthesis of the dark brown pigment eumelanin. Many analogs of α-MSH have been developed, the most investigated being the full length tridecapeptide analog NDP-MSH, also known as afamelanotide, which is at least 100 fold more potent, and considerably more stable than α-MSH. However, NDP-MSH is not selective for the MC1R, and needs to be delivered systemically, which results in non-pigmentary off target effects due to its binding to other melanocortin receptors. To alleviate this problem, we are developing small MC1R selective analogs that can be applied topically rather than administered systemically need to develop. Methodology: Structure activity studies showed that the 6-9 amino acids, His-Phe-Arg-Trp, of α-MSH, are required for its pigmentary effect. We have developed N-capped tetra- and tripeptide analogs of α-MSH, and tested them for their MC1R selectivity, and their potency on cultured human melanocytes. Findings: Some tetra- and tripeptides proved to be highly selective for MC1R and acted as full agonists. Others were not effective in activating the MC1R, suggesting the possibility that they are antagonists. Conclusions and significance: given the central role of MC1R in regulating human pigmentation, analogs of its ligand α-MSH can be developed to either promote MC1R activity to stimulate a tanning response, or to inhibit MC1R activity and reduce pigmentation.

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