5-HT1A/1B receptors as targets for optimizing Pigmentary responses in C57BL/6 mouse skin to stress

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Stress has been reported to induce alterations of skin Pigmentary response. Acute stress is associated with increased turnover of serotonin (5-hydroxytryptamine; 5-HT) whereas chronic stress causes a decrease. 5-HT receptors have been detected in pigment cells, indicating their role in skin pigmentation. To ascertain the precise role of 5-HT in stress-induced pigmentary responses, C57BL/6 mice were subjected to chronic restraint stress and chronic unpredictable mild stress (CRS and CUMS, two models of chronic stress) for 21 days, finally resulting in abnormal pigmentary responses. Subsequently, stressed mice were characterized by the absence of a black pigment in dorsal coat. The down-regulation of tyrosinase (TYR) and tyrosinase-related proteins (TRP1 and TRP2) expression in stressed skin was accompanied by reduced levels of 5-HT and decreased expression of 5-HT receptor (5-HTR) system. In both murine B16F10 melanoma cells and normal human melanocytes (NHMCs), 5-HT had a stimulatory effect on melanin production, dendricity and migration. When treated with 5-HT in cultured hair follicles (HFs), the increased expression of melanogenesis-related genes and the activation of 5-HT1A, 1B and 7 receptors also occurred. The serum obtained from stressed mice showed significantly decreased tyrosinase activity in NHMCs compared to that from non-stressed mice. The decrease in tyrosinase activity was further augmented in the presence of 5-HTR1A, 1B and 7 antagonists, WAY100635, SB216641 and SB269970. In vivo, stressed mice received 5-HT precursor 5-hydroxy-l-tryptophan (5-HTP), a member of the class of selective serotonin reuptake inhibitors (fluoxetine; FX) and 5-HTR1A/1B agonists (8-OH-DPAT/CP94253), finally contributing to the normalization of pigmentary responses. Taken together, these data strongly suggest that the serotoninergic system plays an important role in the regulation of stress-induced depigmentation, which can be mediated by 5-HT1A/1B receptors. 5-HT and 5-HTR1A/1B may constitute novel targets for therapy of skin hypopigmentation disorders, especially those worsened with stress.

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