Pharmacoperone-Mediated Rescue of Melanocortin-4 Receptor: Evaluating SM-001 in Restoring Intracellular cAMP Signaling

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The melanocortin-4 receptor (MC4R) is a G protein–coupled receptor that plays a critical role in energy homeostasis by activating cyclic adenosine monophosphate (cAMP) signaling to suppress appetite and increase energy expenditure. Loss-of-function mutations in MC4R are a major cause of early-onset severe obesity, with most pathogenic variants classified as Class II mutations that are misfolded, retained intracellularly, and unable to activate cAMP signaling. In this study, we evaluated whether SM-001, a small-molecule that can bind MC4R, can function as a pharmacoperone to rescue the misfolded MC4R C84R mutant and restore receptor signaling. The efficacy of SM-001 was compared with the established pharmacoperone ML00253764. HEK293T cells were transfected with wild-type or C84R mutant MC4R using Lipofectamine. The total and cell surface expression of the wild-type and mutant MC4R was assessed by flow cytometry. Transfected cells were treated with SM-001, ML00253764 or 0.1% DMSO (vehicle control) for 24 h at 37oC, followed by stimulation with setmelanotide for 1 h. Cells were then lysed, and intracellular cAMP levels were measured using a cAMP assay kit. Our results demonstrate that the total and cell surface expression of MC4R C84R mutant was significantly lower than the wild-type receptor in transfected HEK293T cells. Treatment with SM-001 significantly increased cAMP production in cells expressing the MC4R C84R mutant, indicating restoration of receptor signaling. These findings suggest that SM-001 has strong pharmacoperone potential and may represent a promising therapeutic approach for rescuing misfolded MC4R variants associated with human obesity.

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