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Functional Rescue of Obesity-causing Human Melanocortin-4 Receptor Mutants: Insights for Pharmacological Chaperon Drugs

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In the past decade, mammalian and human genetic studies revealed that the leptin-regulating pathway plays a critical role in controlling body weight. So far, it has been demonstrated that mutation in seven genes including Leptin (LEP), Leptin Receptor (LEPR), Prohormone 1 (PC1), Pro-Opiomelanocortin (POMC), Melanocortin-4 Receptor (MC4R), and Single-Minded Homolog 1 (SIM1) cause monogenic early-onset obesity for both rodent and human [1]. Among them, MC4R has been identified as a key switch in the leptin-regulating pathway [2-6]. Mutations occurred in the coding region of the MC4R gene represent the most frequent monogenetic form causing human early-onset obesity and thus serve as the best available genetic model to investigate human obesity [7-9]. So far, over 150 mutant MC4Rs has been identified clinically from obese patients of variant ethnic backgrounds and around 6% of the human early-onset obesity was estimated to be caused by the mutated MC4Rs. Functional studies showed that 70% of the mutant MC4Rs are synthesized normally but defective in trafficking onto the cell surface, thus representing the most common defect of mutant MC4Rs [7].

Since many mutations are not likely to affect ligand binding or signaling of the mutant GPCRs directly, they might bind to the ligand and signal once reached the cell surface. Bouvier and collegues pioneered the field of using small molecule antagonists as pharmacological chaperons [10]. These molecules act as folding templates and assist the mutants to fold into the conformations allowing their trafficking onto cell surface. Since then, pharmacological chaperons have been identified for naturally occurring mutations in rhodopsin and Gonadotropin-Releasing Hormone Receptor (GnRHR) [11-14] and wt or laboratory-generated mutants inμ- and δ-opioid receptors, melanin-concentrating hormone receptor 1, as well s V1a and V1b vasopressin receptors [15-19]. The rescuing effect does not depend on specific chemical structure. For example, three different classes of chemicals, including indoles, quinolines, and etythromycinmacrolides, can rescue almost all the naturally occurring GnRHR mutations that cause hypogonadodism [11]. Recently, it has been shown that treatment of patients with nephrogenic diabetes insipidus harboring transportation-defective V2R mutations with the nonpeptide antagonist SR49059 decreased urine volume and water intake [20], proving the clinical utility of pharmacological chaperone drugs.

In 2004, Vos et al. first synthesized a small molecule MC4R antagonist ML00253764 that, late on in 2006, was proved to be an inverse agonist of MC4R [21,22]. In 2009, we were the first group to identify ML00253764 as a MC4R pharmacological chaperone [23]. Since then, several cell-permeable, nonpeptidic small molecule antagonists of MC4R have been examined to determine their ability to rescue the cell surface expression and signaling of intracellularly retained mutant MC4Rs in 2010 [24,25]. The tested compounds belong to structurally different chemical classes and showed various efficacies and potencies towards mutant MC4Rs. Even for a specific compound, clear differences in its ability to rescue the receptor mutants harboring distinct mutations were documented [23,24]. The existence of a large diversity of obesity-related trafficking-defective mutations in MC4R calls into question the ability of a single chemical compound to restore cell surface expression and function to all mutant forms. As a consequence, a MC4R-specific pharmacological chaperone has to be seriously evaluated to determine its rescue profile on distinct mutants, directing the possible personal treatment of the obese-patients bearing a specific MC4R mutation. In common, these small molecules were also found to be able to enhance cell surface expression of WT MC4R and WT MC4R signaling, they may also have potential therapeutic applications for more general obesity without MC4R mutations.

To explore potential rescue strategy to correct the trafficking of the misrouting mutant MC4Rs is of tremendous interest not only in advancing our understanding of obesity pathogenesis caused by MC4R gene mutations but also identifying potential therapeutic approaches to treat these patients. However, the currently examined pharmacological chaperones, as MC4R antagonist/inverse agonist, compete with the natural agonist/antagonist of the receptor for binding, calling into question their potential clinical application. Development of allosteric pharmacological chaperone drug of MC4R thus should become a future direction in this field.

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