The effect of $\sigma_1R$ agonist/wildtype $\sigma_1R$ on abnormal insoluble feature and toxicity of $\sigma_1R$ ALS mutant (E102Q)

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Mutations in sigma-1 receptor ($\sigma_1R$) gene are found in ALS. The $\sigma_1R$ forms oligomers that are regulated by its ligands. However, little is known about the effect of mutations. Here, we transfected motor neuronal NSC-34 cells with $\sigma_1R$-mCherry (mCh), $\sigma_1R^{E102Q}$-mCh or untagged forms to assess detergent solubility and subcellular distribution by immunostaining and FRAP. The oligomeric state was assessed using crosslinker. Wildtype $\sigma_1Rs$ were soluble to detergents, but the mutants were enriched in the insoluble fraction. In the soluble fraction, distribution of mutants appeared in higher sucrose density fractions. Mutants formed aggregates that were co-stained with p62, ubiquitin, and p-PERK, and which had lower recovery in FRAP. Acute treatment with $\sigma_1R$ agonist SA4503 failed to improve recovery, prolonged treatment (48 h) reduced $\sigma_1R^{E102Q}$-mCh insolubility and inhibited apoptosis. While $\sigma_1R$-mCh formed monomers/dimers, $\sigma_1R^{E102Q}$-mCh also formed trimers/tetramers. SA4503 reduced the four types in the insoluble fraction but elevated monomers in the soluble fraction. Co-expression of $\sigma_1R$-mCh reduced $\sigma_1R^{E102Q}$ insolubility. These results suggest that the agonist and wildtype $\sigma_1R$ can modify the detergent insolubility, toxicity, and oligomeric states of $\sigma_1R^{E102Q}$. Pharmacological and genetic approaches may be promising to treat $\sigma_1R$-related ALS.