Loss of ghrelin receptors in dopaminergic neurons in the substantia nigra is critical for Parkinson's disease-like motor dysfunction

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Background: Ghrelin exerts a wide range of physiological actions throughout the body and appears to be a promising target for disease therapy. Endogenous ghrelin receptors (GHSRs) are present in extrahypothalamic sites including the substantia nigra pars compacta (SNc), which is related to phenotypic dysregulation or frank degeneration in Parkinson's disease (PD). In the present study, we evaluated the changes in GHSR expression under the pathology of PD using DA neurons derived from PD-specific iPSCs and investigated the role of ghrelin in nigrostriatal DA neurons in PD.

Methods: We modified the method used to generate a dopamine (DA) neuron-enriched culture by treating induced pluripotent stem cell (iPSC)-derived cells with several small molecules that lead to the formation of ventral midbrain DA cells and evaluated the changes in GHSR expression in DA neurons derived from PD-specific iPSCs. We next used isogenic iPSC lines mimicking loss of function of the parkin gene (PARK2) through CRISPR Cas9 technology in the healthy control iPSC line 201B7 and evaluated the changes in GHSR expression in DA neurons derived from PARK2-KIKO iPSC lines. Furthermore, we confirmed that the inhibition of GHSR in DA neurons of the SNc induced motor dysfunction.

Results: We found a dramatic decrease in the expression of GHSR in PD-specific iPSC-derived DA neurons generated from patients carrying PARK2 mutations compared to those from healthy controls. Consistently, a significant decrease in the expression of GHSR was found in DA neurons of isogenic PARK2-iPSC lines that mimicked loss of function of the PARK2 gene through CRISPR Cas9 technology. To evaluate the in vivo effect of the blockade of GHSR1a, a guide cannula was implanted into the SNc for microinjection. Bilateral microinjection into the SNc of the selective GHSR1a antagonist [D-Lys3]-GHRP6 in normal mice produced cataleptic behaviors related to dysfunction of motor coordination.

Conclusion: These findings suggest that the down-regulation of GHSRs in SNc-DA neurons induced the initial dysfunction of DA neurons, leading to extrapyramidal disorder under PD.