学位論文の要旨

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主論文の題名

Systemic administration of valproic acid and zonisamide promotes differentiation of induced pluripotent stem cell–derived dopaminergic neurons

主論文の要旨

Cell replacement therapy using embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) is a promising strategy for the treatment of neurologic diseases such as Parkinson's disease (PD). However, a limiting factor for effective cell transplantation is the low survival rate of grafted cells, especially neurons. In this study, we modified the host environment and investigated whether the simultaneous administration of soluble factors can improve the survival and differentiation of murine iPSC-derived dopaminergic (DA) neurons in host brains. With the goal of applying this technology in clinical settings in the near future, we selected drugs that were already approved for clinical use. The drugs included two commonly used anti-convulsants, valproic acid (VPA) and zonisamide (ZNS), and estradiol (E2), also known as biologically active estrogen. Following neural induction of murine iPSCs, we collected neural progenitor cells (NPCs) by sorting PSA-NCAM+ cells, then treated the PSA-NCAM+ cells with drugs for 4 days. An immunofluorescence study revealed that 0.01mM and 0.1mM of VPA and 10nM of E2 increased the percentage of tyrosine hydroxylase+ (TH: a DA neuron marker) cells *in vitro.* Furthermore, 0.1mM of VPA increased the percentage of TH+ cells that simultaneously express the midbrain markers FOXA2 and NURR1. Next, in order to determine the effects of the drugs *in vivo,* the iPSC-derived NPCs were transplanted into the striata of intact SD rats. The animals received intraperitoneal injections of one of thedrugs for 4 weeks, then were subjected to an immunofluorescence study. VPA administration (150 mg/kg/daily) increased the number of NeuN+ post-mitotic neurons and TH+ DA neurons in the grafts. Furthermore, VPA (150 mg/kg/daily) and ZNS (30 mg/kg/daily) increased the number of TH+ FOXA2+ midbrain DA neurons. These results suggest that the systemic administration of VPA and ZNS may improve the efficiency of cell replacement therapy using iPSCs to treat PD.

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