뇌신경재활
발표일시 및 장소 : **10 월 26 일(금) 15:15-15:25 Room C(5F)**

OP2-2-7

Enriched Environment Ameliorates Oxidative Stress and Olfactory Dysfunction in a Parkinson's Model

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Introduction
Parkinson's disease (PD) features nonmotor symptoms such as olfactory dysfunction referred to as hyposmia, an initial sign of disease progression. Metabolic dysfunction can contribute to neurodegenerative diseases, and various xenobiotics and endogenous compounds are also involved in the pathogenesis of PD. Although aerobic exercise was found to induce preservation or improvement in olfactory function in PD patients in a recent study, the exact underlying mechanism for this effect is not clear. We aimed to investigate the influence of an enriched environment (EE) on olfactory dysfunction especially via metabolic pathways related to detoxification enzymes.

Method
Eight-month-old PD transgenic (Tg) mice overexpressing human A53T a-synuclein (a-syn) were randomly allocated to an EE or standard conditions for 2 mo. Buried food test was performed twice on mice at 8 and 10 mo of age. Reverse transcription polymerase chain reaction (PCR) and real-time quantitative PCR were done to evaluate expression of the detoxification enzymes at 10 and 13 mo in the olfactory bulb of PD. We performed immunohistochemical staining of iNOS to evaluate the level of oxidative stress in olfactory bulb of 10-mo-old WT, PD control, and PD EE mice.

Results
The buried food test showed that EE group had significantly improved olfactory function compared to the control group. Reverse transcription polymerase chain reaction (PCR) and real-time quantitative PCR showed that expression of the detoxification enzymes—cytochrome P450 family 1 subfamily A member 2, paraoxonase 1, alcohol dehydrogenase 1, UDP glucuronosyltransferase family 2 member A1 complex locus, aldehyde oxidase homolog 2, and aldehyde glutathione peroxidase 6—was significantly increased in the olfactory bulb (OB) of the PD control group, but these enzymes were normalized in the EE

group. Immunohistochemical staining of the OB showed that oxidative stress and nitrated a-syn were significantly increased in the control group but decreased in the EE group.

Conclusion

In a Tg mouse model of PD that overexpressed human A53T a-syn, exposure to an EE reduced oxidative stress and nitrated a-syn, resulting in normalized detoxification enzymes and amelioration of olfactory dysfunction.

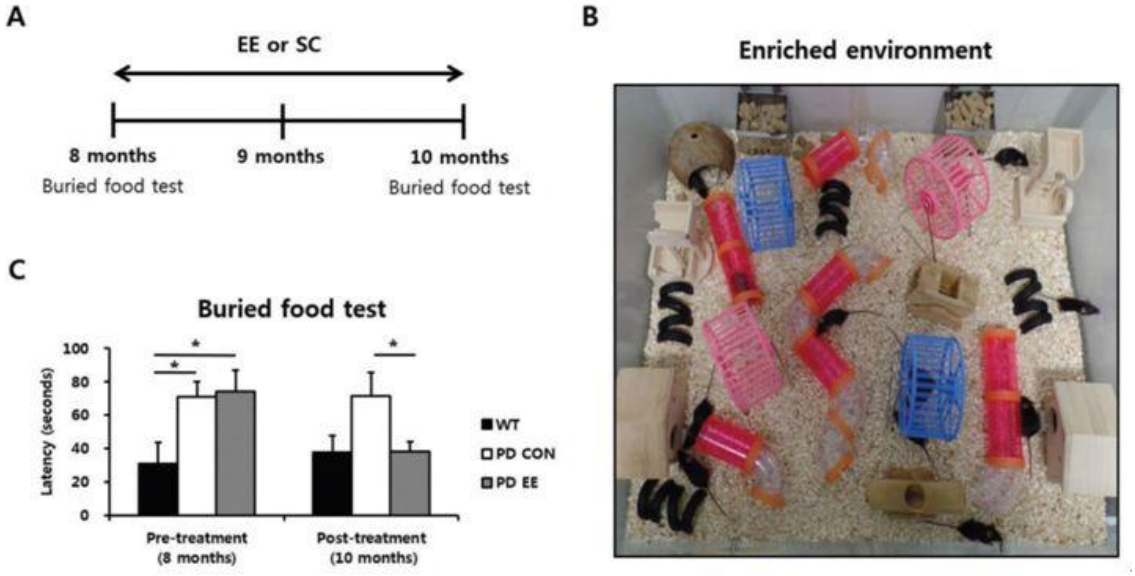

Figure 1. Experimental design and effect of an enriched environment on olfactory dysfunction in Parkinson's disease. (A) Schematic timeline of the experiment in a mouse model of PD. (B) An image of EE. (C) Buried food test result. The latency time of finding food in PD control group (N=14, 71.0+9.2 sec, P < 0.05) and PD EE group (N=11, 74.2+12.8 sec, P<0.05) significantly increased compared to WT group (N=8, 30.7+4.6 sec) at 8 mo of age. The result of latency time of find food at 10 mo of age showed that the PD EE group (37.9+6.1 sec, P<0.05) significantly decreased compared to PD control group (71.3+14.2 sec). Abbreviations: PD=Parkinson's disease; EE=enriched environment; WT=wild type. *P<0.05 is based on a one-way ANOVA followed by a post hoc test.

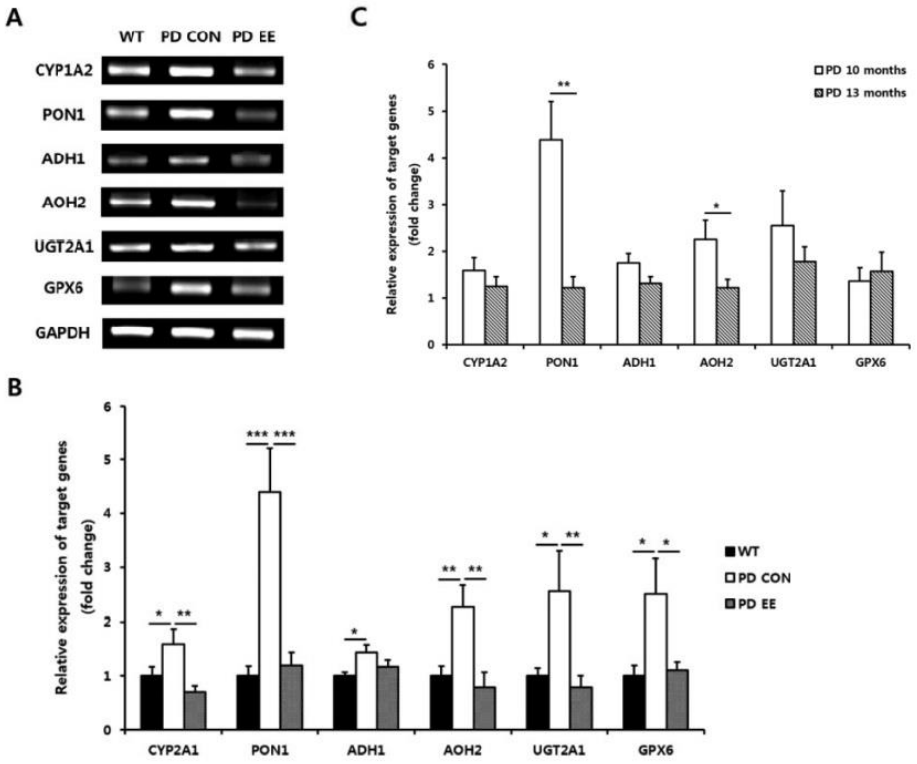

Figure 2. Expression of genes related with detoxification enzymes in the olfactory bulb. (A) RT-PCR analysis of 6 genes related to detoxification enzymes in the OB of PD mice at 10 mo of age. (B) Quantitative comparison of gene expression in the PD control (N=5) and PD EE group (N=5) relative to WT mice (N=5) at 10 mo determined by RT-qPCR. The expression of CYP1A2 (1.59-fold), PON1 (4.39-fold), ADH1 (1.43-fold), AOH2 (2.26-fold), UGT2A1 (2.55-fold), and GPX6 (2.50-fold) was significantly increased in the PD control group compared to the WT group. However, the expression of CYP1A2 (0.70-fold), PON1 (1.20-fold), ADH1 (1.17-fold), AOH2 (0.79-fold), UGT2A1 (0.79-fold), and GPX6 (1.10-fold) was decreased in the PD EE group compared to the PD control group. *P<0.05 and **P<0.01 by an independent t test. (C) Gene expressions of early stage mice, 10 mo of age, of PD mice (N=5) relative to the same age of WT mice (N=5) and that of PD mice (N=7) in late stage, 13 mo of age, relative to the same age of WT mice (N=5) were compared. PD mice in late stage showed the decrease in CYP1A2 (0.78-fold), PON1 (0.28 fold), ADH1 (0.75-fold), AOH2 (0.54-fold), UGT2A1 (0.70-fold), and GPX6 (1.16-fold) compared to the PD mice in early stage. *P<0.05, **P<0.01, and ***P<0.001 by a one-way ANOVA followed by a post hoc test.

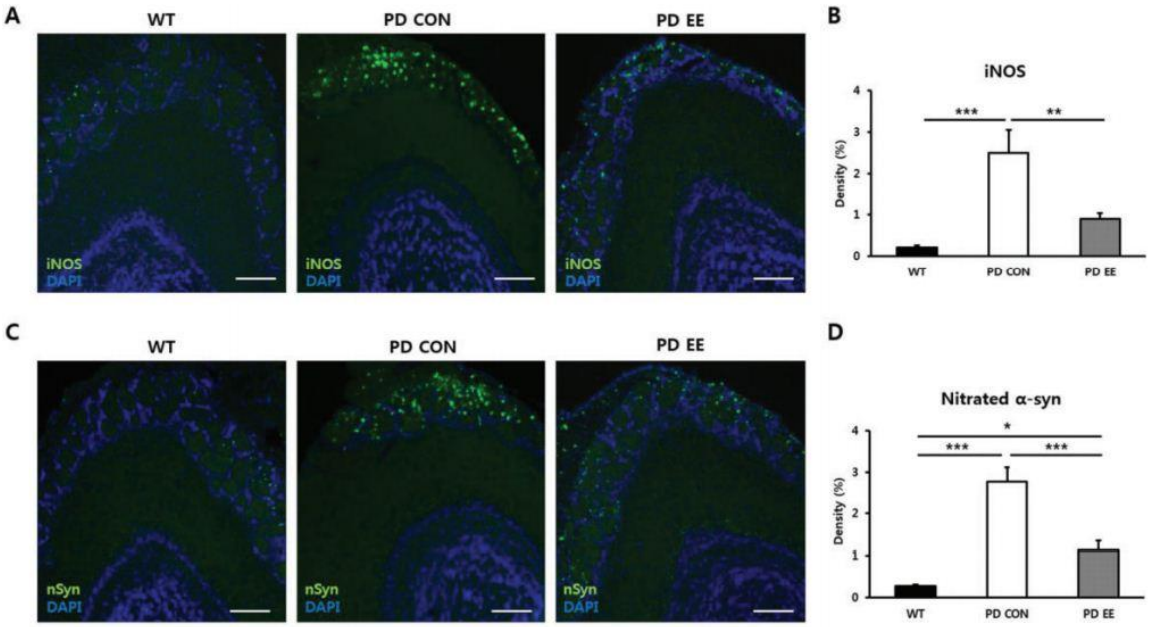

Figure 3. An enriched environment ameliorates oxidative stress and nitrated a-syn in PD. (A) Images of the iNOS immunohistochemistry staining in the glomerular layer of the olfactory bulb. (B) The density of iNOS was significantly higher in PD control group (2.5+0.53%, P<0.001) than in WT group (0.2+0.06%). However, the density of nitrated a-syn was significantly lower in PD EE group than in both PD control group and WT group based on a one-way ANOVA (1.1+0.21%, P<0.001, P<0.05, respectively). Scale bars=200 mm. Abbreviations: a-syn=human A53T a-synuclein; PD=Parkinson's disease; iNOS=inducible nitric oxide; WT=wild type; EE=enriched environment; ANOVA=analysis of variance. *P<0.05, **P<0.01, and ***P<0.001 by a one-way ANOVA followed by a post hoc test.