P1-n27 Synergistic protection of dopamiergic neuron by an allosteric potentiating ligand

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Parkinson's disease (PD) is a progressive neurodegenerative disease caused by a loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Recent studies have reported that the stimulation of nicotine acetylcholine receptor (nAChR) is considered to confer a neuroprotective effect and decreases a risk of PD. Galantamine is an acetylcholinesterase inhibitor and allosteric potentiating ligand (APL) for nAChRs. However, the effect of galantamine on the neuroprotection through nAChRs is unknown. In this study, we used a 6-OHDA rat model, which showed dopaminergic neuronal loss in the SNpc. We found that α7nAChRs were expressed on the dopaminergic neurons and nicotine injection prevented the dopamiergic neuronal loss in 6-OHDA rat model. Although galantamine injection alone did not show any neuroprotective effect, co-administration of galantamime with nicotine enhanced the neuroprotective effect of nicotine. These results suggest that allosteric modulation α7nAChRs by galantamine enhances the neuroprotective effect of nicotine against 6-OHDA-induced dopaminergic neuronal loss. Thus, there is a possibility that allosteric modulation of nAChR has a therapeutic potential for PD.

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P1-n28 The endoplasmic reticulum stress sensor, ATF6α, protects against 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-induced dopaminergic neuronal death in a p38 Mitogen-Activated Protein Kinase dependent manner

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Oxidative stress and endoplasmic reticulum (ER) stress are thought to contribute to the pathogenesis of various neurodegenerative diseases including Parkinsons disease (PD), however, the relationship between these stresses remains unclear. ATF6α is an ER-membrane-bound transcription factor that is activated by protein misfolding in the ER and functions as a critical regulator of ER quality control proteins in mammalian cells. The goal of this study was to explore the cause–effect relationship between oxidative stress and ER stress in the pathogenesis of neurotoxin-induced model of PD. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a dopaminergic neurotoxin known to produce oxidative stress, activated ATF6α and increased ER chaperones and ER associated degradation (ERAD) component in dopaminergic neurons. Importantly, MPTP induced formation of ubiquitin-immunopositive inclusions and loss of dopaminergic neurons more prominently in mice deficient in ATF6α than in wild-type mice. Cultured cell experiments revealed that 1-Methyl-4-phenylpyridinium (MPP+)-induced oxidative stress not only promoted phosphorylation of p38 Mitogen-Activated Protein Kinase (p38MAPK) but also enhanced interaction between phosphorylated p38MAPK and ATF6α, leading to increment in transcriptional activator activity of ATF6α. Thus, our results revealed a link between oxidative stress and ER stress by showing the importance of ATF6α in the protection of the dopaminergic neurons from MPTP that occurs through oxidative stress-induced activation of ATF6α and p38MAPK-mediated enhancement of ATF6α transcriptional activity.

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P1-o01 Mapping of brain acetylcholinesterase alterations in Lewy body disease by PET

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Objective: To characterize brain cholinergic deficits in Parkinson's disease (PD), PD with dementia (PDD), and dementia with Lewy bodies (DLB). **Methods**: Participants included 18 patients with PD, 21 patients with PDD/DLB and 26 healthy controls. The PD group consisted of nine early PD patients, each with a disease duration of less than 3 years, five of whom were de novo PD patients, and nine advanced PD patients, each with a disease duration greater than or equal to 3 years. The PDD/DLB group consisted of 10 PDD patients and 11 DLB patients. All subjects underwent PET scans with N-[11C]-methyl-4-piperidyl acetate to measure brain acetylcholinesterase (AChE) activity. Brain AChE activity levels were estimated voxel-by-voxel in a three-compartment analysis using the arterial input function, and compared among our subject groups through both voxel-based analysis using the statistical parametric mapping software SPM5 and volume-of-interest analysis. **Results**: Among PD patients, AChE activity was significantly decreased in the cerebral cortex and especially in the medial occipital cortex (% reduction compared with the normal mean = −12%) (FDR-corrected p-value < 0.01). PDD/DLB patients, however, had even lower AChE activity in the cerebral cortex (% reduction = −27%) ($p < 0.01$). There was no significant difference either between early PD and advanced PD groups or between DLB and PDD groups in the amount by which regional AChE activity in the brain was reduced. **Conclusions**: Brain cholinergic dysfunction occurs in the cerebral cortex, especially in the medial occipital cortex. It begins in early PD, and is more widespread and profound in both PDD and DLB.

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P1-o02 Mechanisms underlying locomotor asymmetry in the rat induced by stimulation of the medial forebrain bundle

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Intense intracranial self-stimulation (ICSS) can be achieved by electrical stimulation of the medial forebrain bundle (MFB), which leads to repetition of gratifying action in laboratory animals. As MFB is a bundle of dopaminergic axons both from ventral tegmental area and substantia nigra, we aim to study the effect of MFB-stimulation on rat's locomotor features. In stereotaxic surgery, stimulus electrode was placed in the MFB (AP: −3.6; ML: +1.8; DV: +9.2), local field potentials (LFPs) recording electrodes were inserted into bilateral primary motor cortex (MI, AP: +2.5; ML: ± 3.0; DV: +1.2) and spike recording tetrodes were targeted at homolateral entopeduncular nucleus (EP, AP: −2.4; ML: −2.8; DV: +7.6). Behavior test in which rat had to make left or right choice (eight-arm radial maze) was investigated when sending continual stimulation to unilateral MFB. We found that rat made much more contralateral turns than homolateral per min (contralateral: 7.3 ± 0.5; homolateral: 0.43 ± 0.12, $P < 0.001$) when exited an arm, which suggested a significant locomotor asymmetry. Applying Wavelet Packet Transform to make time-frequency analysis of MI-LFPs revealed that 100-400 ms after unilateral MFB-stimulation, the power spectrum distribution of homolateral MI-LFPs (especially β band) was significantly increased; the increase of contralateral appeared much later (600-700 ms) and less significant. Peristimulus time histogram analysis of EP-GABAergic neurons' spike rasters showed that before unilateral MFB-stimulation, homolateral EP neurons maintained a stable firing rate; 200-500 ms after stimulation, 87/96 neurons were motivated and sustained much higher discharge frequency ($P < 0.001$). Overall, this study reveals that besides gratifying effect, MFB stimulation