[課程―２]

審査の結果の要旨

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Dopaminergic regulation is dependent on D2-like receptors, which influence brain morphology and function. The dopamine D2 receptor gene (DRD2) encodes the D2 subtype of the dopamine receptor and the expression of D2 receptors is modulated by a DRD2/ANKK1-Taq1A polymorphism (rs1800497). The DRD2 Taq1A polymorphism, a single nucleotide polymorphism (SNP), potentially affects the concentrations of synaptic dopamine. The two alleles of the DRD2 Taq1A polymorphism are referred to as A1 and A2. The A1 allele of the DRD2 gene Taq1A polymorphism had been associated with a low D2 receptor density.

This study verified a potential association between the DRD2 Taq1A polymorphism (genotyped utilizing the Taqman Allelic Discrimination Assay System) and the morphology of WM in young healthy subjects, using voxel based morphology (VBM) analysis. Data from 765 healthy, right-handed individuals (425 male and 340 female; 20.7 ± 1.8 years of age) recruited by University advertisement were used in this study. Then the analysis of covariance (ANCOVA) was conducted to test the difference in regional WM volume among DRD2 Taq1A polymorphism carriers (A1 carriers: 443, A1 non-carriers: 323) by T1 weighted image. The below results were derived.

In a voxel-by-voxel comparison, after correcting for age, sex, and TIV, several regions show significant decreased white matter volume (WMV) in A1 carriers (A1/A1, A1/A2) compared to non-A1 carriers (A2/A2). Significant differences detected between A1 carriers and non-A1 carriers include regions that can roughly be divided into two clusters. A large region includes fifteen clusters, while a small region includes four clusters.

The TFCE method yielded decreased WM volumes (FWE corrected $P < 0.05$) in regions including the bilateral thalamus proper, the cerebral WM around the left lateral ventricle, the left parietal operculum, the right ventral DC, the left fusiform gyrus, and the left hippocampus in A1 carriers compared to non-A1 carriers.

In the large region clusters, WMV of A1 carriers was significantly decreased in seven clusters adjacent to the bilateral thalamus in the first anatomical clusters identified in the ANCOVA analysis. Two were located in the right thalamus. The other five clusters were identified in the left thalamus. A second anatomical cluster was identified in a WM region adjacent to the parietal operculum. As the third anatomical region, five clusters of WM regions around the lateral ventricle were observed. As the

fourth anatomical clusters, three WM regions around the lateral ventricle were identified. The fifth anatomical cluster was located in a WM region around the Ventral DC.

Smaller clusters which showed significant differences of decreased WM volume between A1 carriers and A1 non-carriers were observed in regions of the limbic area. There were significant differences of decreased WM volume between A1 carriers and A1 non-carriers in the frontal lobe WM regions near the border between the fusiform gyrus and the hippocampus. Two clusters are located within the left fusiform gyrus. Another two clusters were detected in the WM regions around the left hippocampus.

There were no greater regions of WM volume in A1 carriers compared to the A2/A2 - carrier in $P < 0.05$ for multiple comparison (voxel - level FWE) for whole brain analysis.

According to this investigation this study confirms an effect of the DRD2 polymorphism on white-matter volume in the regions including the thalamus-mediated cortico-subcortical interactions and limbic regions, which is thought to be strongly related to the DRD2 gene expression. The results support the possibility that the differences of dopaminergic effects caused by DRD2 Taq1A Polymorphism are related to WM volume in the regions including the thalamus-mediated cortico-subcortical interactions and the limbic system and may help to clarify the relationship between neural networks underlying plasticity and WM connections. Taken together, this study proposes an important possibility that the WM structure or its components including myelination around the thalamus and the limbic system may have decreased rWMV in A1 carriers compared to A1 non-carriers. Therefore, the author of the present study deserves the award of doctor’s degree.