学 位 論 文 の 要 旨

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学 位 論 文 名　Serotonin-1A Receptor C-1019G Polymorphism Affects Brain Functional Networks

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論 文 内 容 の 要 旨

INTRODUCTION

5-Hydroxytryptamine (5-HT) is commonly known as serotonin. Human positron emission tomography (PET) studies have demonstrated that serotonin signalling is modulated by a 5-HT1A receptor gene C(-1019)G polymorphism. Clinical studies have also reported that the -1019G allele is associated with fear expression, trait anxiety, schizophrenia, major depression and suicide. Therefore, genetic variations in the 5-HT1A receptor appear to play a critical role in affective disorders and need further investigation.

Resting-state functional magnetic resonance imaging (fMRI), a noninvasive, nonradiation means for mapping the functional connectivity (FC) of the human brain, has become a promising avenue to investigate the neurophysiological basis of human brain functions. In an animal study, an increase of FC in the cerebral cortex, hippocampus, amygdala and dorsomedial thalamus was observed after giving 5-HT1A receptor agonist, 8-OH-DPAT. Human studies, using combined PET and resting-state fMRI, have also confirmed that the raphe nuclei have significant positive FC within brain regions involved in cognitive and emotion processing and that the 5-HT1A receptor binding potential appears to predict the activity of default mode network. It has been demonstrated that 5-HT1A receptor modulates brain FC. Yet, it is unknown whether this modulation is affected by the 5-HT1A receptor genetic variant.

During emotional processing tasks, the 5-HT1A C(-1019)G polymorphism has been shown to impact the activity of forebrain targets, such as the amygdala, insula and anterior cingulate. Interestingly, as in affective function, the G allele in healthy participants is also associated with a decrease in cognitive. We therefore hypothesised that the C(-1019)G 5-HT1A receptor polymorphism is a potential neurochemical modulator for FC in human brain networks that

associate with emotional and/or cognitive processing.

In the current study, we aim to fill this gap in the known effects of 5-HT1A C(-1019)G variant on resting-state brain networks. We examined three main large-scale networks known to underlie a broad range of human emotional-cognitive operations: the default mode network (DMN), which is a network important in self-referential activities; the salient network (SN), which is critical for emotional awareness; and the central executive network (CEN), a network associated with emotional regulation and cognitive control of attention.

MATERIALS AND METHODS

Participants

The current study included 99 healthy participants (65males, 34 females). The mean age of the participants was 53.9 ± 13.1 (SD) years old. The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was obtained from all subjects.

Genotyping for the 5-HT1A Receptor

Genotypic analysis for 5-HT1A receptor (1019C/G) polymorphisms was carried out using the TaqMan SNP Genotyping Assay system (Assay ID: C_11904666_10; Applied Biosystems, Foster, CA, USA). Briefly, fasting venous blood samples were obtained from all study participants. Genomic DNA was extracted from peripheral blood leukocytes using a standard phenol/chloroform method. Genotyping of the C-1019G polymorphism in the 5-HT1A receptor was amplified using polymerase chain reaction.

Image Acquisition

All functional and structural imaging data were acquired using a Siemens 1.5T MRI scanner. Participants were instructed to remain still with eyes closed, try to avoid engaging into any thinking and to not fall asleep for 5min resting-state fMRI scan.

Functional Imaging Processing

After standard data preprocessing in Statistical Parametric Mapping 12, the iterative Seed-Based correlation analysis (SBA) was performed to establish the DMN, SN, and CEN. Seed-to-voxel FC analyses were performed using the CONN functional connectivity toolbox v16. Second level analyses of two sample t-tests were carried out using SPM12 to investigate the effect of 5-HT1A receptor polymorphisms on FC, sex and age were taken as covariate. SPM12 default threshold of $p < 0.001$ was set for bidirectional explorations of connectivity. Results of exploratory analyses were considered significant if clusters survived FWE correction at $p < 0.05$.

RESULTS AND DISCUSSION

Genotyping

99 samples without abnormal structural MRI findings were used in the analyses of the effect of 5-HT1A receptor polymorphism (CC:59, CG:28, GG:12) on brain FC. We dichotomised subjects into G-carriers group and C-homozygotes group. There were no significant differences in age, gender and neuropsychological scores between G-carrier and C-homozygote groups.

Resting-state FC Networks

The DMN, SN, and CEN were assessed using seed-based analysis. The FC analysis showed substantial involvement of the posterior cingulate, medial prefrontal and lateral parietal cortices in the DMN. The SN consisted of the dorsal anterior cingulate cortex and bilateral insula, whereas the CEN involved the dorsolateral prefrontal cortex and other regions such as the bilateral superior parietal and inferior temporal gyri.

Comparison of Resting-state FC Between G-homozygote and C-carrier Groups

We compared resting-state FC between G-carrier and C-homozygote groups. G-carriers showed decreased cortical FC of the left dorsolateral prefrontal cortex (L-dlPFC, cluster-level FWE-corrected, $p = 0.004$) and ventromedial prefrontal cortex (vmPFC, cluster-level FWE-corrected, $p = 0.016$) for the DMN. In the SN, there was a significant decrease in FC at the vmPFC (cluster-level FWE-corrected, $p = 0.001$) and subgenual anterior cingulate cortex (sgACC, cluster-level FWE-corrected, $p = 0.002$) was also observed in the G-carrier group. There were no significant differences in FC within the CEN between the two groups.

Our results confirmed that the 5-HT1A receptor modulates FC in the DMN and extended the results of previous neuroimaging studies by showing a strong effect of this single nucleotide polymorphism on the DMN and SN. In line with previous reports, our finding of decreased FC of the prefrontal cortex area and sgACC within the DMN and SN in the G-carrier group suggests a central role for 5-HT1A receptor genetic polymorphism in the modulation of front-limbic circuit function.

Existing evidence has confirmed that the abnormal FC in the vmPFC region is associated with the pathology of affective disorders. However, there is no consistent pattern of abnormalities in large-scale functional brain networks. Our results provide the first evidence to associate the 5-HT1A receptor C(-1019)G polymorphism with the hypoconnectivity of vmPFC within DMN and SN. This could contribute to the understanding of neural circuitries underlying the influence of -1019G allele on complex FC alteration implicated with affective disorders.

We expected to find associations between 5-HT1A receptor gene variants with FC in DMN, SN, and CEN. However, we did not observe any differences in the FC of the CEN. Consistent with our result, a task-based fMRI study which investigated the association of 5-HT1A C(-1019)G polymorphism with brain region activity in patients with panic disorder also observed a decreased activity of vmPFC but not dlPFC in -1019G allele carriers. Thus, the polymorphism of 5-HT1A receptor might not directly impact higher cognitive processing in healthy human brains.

CONCLUSION

We found that 5-HT1A receptor polymorphism modulates brain FC of the DMN and SN, and that G-carriers have decreased FC activity in the regions related to emotional processing. Our findings suggest that 5-HT1A receptor polymorphism might impact the emotional regulation process, thus offering new evidence and strategic insight into the underlying mechanisms of 5-HT1A receptor genetic susceptibility for affective disorders.