Impact of serotonin transporter gene polymorphism on brain activation by colorectal distention

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ABSTRACT
Background and aims: Determining the gene that plays a key role in brain–gut interactions is a crucial step for clarifying the pathophysiology of irritable bowel syndrome (IBS). We previously reported that the 5-hydroxytryptamine transporter gene-linked polymorphic region (5-HTTLPR) is related to anxiety in subjects with IBS. The amygdala is more activated during fearful face recognition in individuals with the s allele of 5-HTTLPR. Here, we tested our hypothesis that 5-HTTLPR differentially activates brain regions with colorectal distention in humans.

Methods: We enrolled 28 subjects without any organic disease. The study was approved by the Ethics Committee and all subjects gave written informed consent. DNA was extracted from the peripheral blood. The genotype of 5-HTTLPR was determined using polymerase chain reaction. Age, sex, diagnosis-matched individuals with the s/s genotype (n = 14) and individuals with the l allele (genotypes l/s, l/l, l/extra-l, n = 14) were compared. A barostat bag was inserted to the colorectum and was intermittently inflated with no (0 mm Hg), mild (20 mm Hg), or intense (40 mm Hg) stimulation on a random order. Radioactive H2 [15O] saline was injected at bag inflation and then positron emission tomography was performed. Changes in rCBF were analyzed using statistical parametric mapping.

Results: Individuals with the s/s genotype showed a significantly larger increase in rCBF by colorectal distention from 0 mm Hg to 40 mm Hg than individuals with the l allele. The significantly more activated brain regions in individuals with the s/s genotype were the left anterior cingulate cortex and right parahippocampal gyrus (p < 0.0001). The increase in rCBF by colorectal distention of 20 mm Hg compared with 0 mm Hg was significantly larger in the left orbitofrontal cortex of individuals with the s/s genotype than that of individuals with the l allele (p < 0.0001).

Conclusion: These data suggest that individuals with a weak function of serotonin transporter respond to gut signals more in emotion-regulating brain regions. Functional gene polymorphism may partially predict the individual effect of a selective serotonin reuptake inhibitor on visceral pain.

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Introduction

Recent concepts of brain science have started to propose that the formation of emotion initially depends on interoception (Craig, 2002). Among many modalities of interoception, visceral activation and visceral perception are key physiological events for clarifying the mechanism of irritable bowel syndrome (IBS), a prevalent prototype of functional gastrointestinal disorders (Mayer et al., 2006). Research on visceral perception is not only limited to gastroenterology but also has great impact on conceptualization of the role of the body as the origin of emotion, as indicated by the symbolic words “gut feeling” (Bechara et al., 2005). Furthermore, visceral perception is one of the demonstrable phenomena for exploring the origin of complex emotion and consciousness in humans (Lane, 2000, Bud Craig, 2009). Based on these studies, it is acceptable to point out that clarification of the brain processing of visceral perception has great impact on neuroscience.

Our previous study using positron emission tomography (PET) demonstrated that colonic stimulation increases regional cerebral...
blood flow (rCBF) in the anterior cingulate cortex (ACC) and prefrontal cortex (PFC), showing correlation with increased anxiety (Hamaguchi et al., 2004). In a functional magnetic resonance imaging (fMRI) study, IBS subjects showed stronger activation of the ACC in response to intense rectal distension than control subjects (Mertz et al., 2000). Imaging data on depressive disorders suggest that one of the common regions of brain activation is the ACC (Ressler and Mayberg, 2007). Subjects with major depressive disorder compared with healthy controls have also shown increased activation of the ACC during anticipation of pain relative to nonpainful stimuli (Strigo et al., 2008). With regard to intrinsic functional connectivity, a significant difference for dorsal to rostral ACC connectivity between patients with depressive disorder and controls in terms of higher connectivity in patients has also been reported (Schlösser et al., 2008). Therefore, increased activity of the ACC is one of the key features of interoception-induced negative emotion.

Serotonin (5-hydroxytryptamine; 5-HT) plays a crucial role in multiple brain function including negative emotion (Kandel, 2000). Serotonin is released from serotonergic nerve terminals which distribute almost throughout the brain and mainly originate from the raphe nuclei in the brain stem. Among the brain regions, the limbic system (i.e., cingulate cortex, hippocampus, amygdala, orbitofrontal cortex (OFC), and hypothalamus) are densely innervated by serotonergic neurons. Serotonin has pathogenic roles in terms of the formation of negative mood typically characterized by depression and anxiety. Depressive disorders and anxiety disorders are thus treated with many agents that normalize serotonergic neurotransmission (Delgado et al., 1990). The serotonin transporter (5-HTT) regulates serotonergic activity and is the target of selective serotonin reuptake inhibitors (SSRIs), which are widely used antidepressants (Frazer, 2001). The human 5-HTT gene (5SLC6A4) is located on chromosome 17q12, and a variant in the upstream promoter region of the 5-HTT gene has been identified (Lesch et al., 1996). The 5-HTT linked promoter region (5-HTTLPR) polymorphism with long (l, 528 bp) and short (s, 484 bp) forms affect the expression and function of 5-HTT. Those with the s allele of this polymorphism are associated with lower transcriptional efficiency of the promoter than the l allele, leading to a lower 5-HTT expression and a lower cellular uptake of serotonin in the presynaptic nerve terminals of serotonergic neurons. This results in a higher serotonin concentration in the synaptic cleft and increases susceptibility to negative mood in individuals with the s gene. In actuality, individuals with the s gene are at significantly greater risk for major depressive disorder following repeated adult stress or childhood trauma (Caspi et al., 2003). Hariri et al. (2002) reported that individuals with the s allele of 5-HTTLPR, which has been associated with reduced 5-HTT expression and function and increased fear and anxiety-related behaviors, show greater amygdala neuronal activity, as assessed by blood oxygen level-dependent MRI, in response to fearful stimuli than individuals homozygous for the l allele. Functional analysis of the ACC and amygdala during perceptual processing of fearful stimuli demonstrated tight coupling as a feedback circuit implicated in the extinction of negative effect, and s allele carriers showed relative uncoupling of this circuit (Pezawas et al., 2005). The magnitude of coupling inversely predicted almost 30% of variation in temperamental anxiety. Taken together, these data suggest that 5-HTTLPR at least in part may predict the function of prefrontal-limbic circuits, especially of the ACC and amygdala, during emotional formation.

Although interoception is considered to be the essential process of emotional formation, most previous studies used visual and cognitive tasks to demonstrate brain processing. To date, no studies on the influence of 5-HTTLPR on brain processing of visceral perception have been reported. We therefore tested our hypothesis that 5-HTTLPR differentially activates brain regions with colorectal distention in humans.

Subjects and methods

Subjects

Twenty-eight adult Japanese subjects without organic diseases or psychiatric disorders were enrolled in the study. Psychiatric disease was excluded through an unstructured clinical interview conducted by a board-certified specialist of the Japanese Society of Psychosomatic Medicine and via a structured interview using the Structured Clinical Interview (First et al., 1996, 2001) for DSM-IV (American Psychiatric Association, 2000). Subjects were genotyped as described below. Individuals with the s/s genotype (n = 14, s group) and those with the l allele (genotype l/s, n = 10; genotype l/l, n = 2; genotype l/extra-l, n = 2; total n = 14, l group) were compared. All subjects were right-handed. Age, sex, gastrointestinal symptoms, and the stimulated site did not differ among groups (Table 1). Each group was composed of 11 healthy subjects and 3 IBS subjects who fulfilled the Rome III criteria (Longstreth et al., 2006). This study was approved by the Tohoku University Ethics Committee and subjects provided written informed consent.

Genotyping

A plastic catheter was inserted into the left forearm vein of each subject and saline was infused at a speed of 1.6 ml/min. Peripheral blood was sampled with a heparinized syringe. Genotyping was performed using the same methods as in our previous report (Mizuno et al., 2006). In brief, DNA was extracted from lymphocytes. The polymorphism in the regulatory region of the 5-HTT gene was genotyped by polymerase chain reaction (PCR). PCR-amplification was carried out using primer pairs reported by Lesch et al. (1996) (5'-GCC TTT GCC CTT CTC ATG CG-3' and 5'-GAC GGA CTC AGC TGG ACA ACC AC-3'). A 25 μl PCR reaction consisted of a 0.2 μM concentration of each primer, 1.5 mM MgSO₄, 0.2 mM each of deoxynucleotide triphosphate, 1× PCR Amplification Buffer, 2.5 μl of Platinum Taq DNA Polymerase, and 1× PCR Enhancer Solution (GIBC0 BRL, Life Technologies Inc., Rockville, MD, USA). After initial denaturation at 95°C for 2 min, amplification was performed using 35 cycles at 95°C for 30 s, 60°C for 30 s (annealing), and 68°C for 1 min, followed by a final elongation at 68°C for 3 min. The amplification products were separated on 2% agarose gel by electrophoresis and classified as long and short alleles.

To ensure genotype accuracy, sequence analysis of 5-HTTLPR genes was performed on PCR fragments which were amplified according to the previously described protocol. PCR products were purified from agarose gel using a QIAquick Gel Extraction kit (QIAGEN, Hilden, Germany). Amplimers were sequenced directly using the ABI Prism dRodamine ™ Terminator Cycle Sequencing Ready Reaction kit (PE Applied Biosystems, Foster City, CA, USA), and excess dye terminators were removed using CENTRI-SEP Columns (PRINCETON SEPARATIONS, Adelphia, NJ, USA). Automated sequencing was performed on an ABI 310 Genetic Analyzer (PE Applied Biosystems). All procedures

<table>
<thead>
<tr>
<th>Number</th>
<th>Age (mean±SD)</th>
<th>Sex (male/female)</th>
<th>Protocol (colon/rectum)</th>
<th>Diagnosis (normal/IBS)</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>23.9± 3.5</td>
<td>11/3</td>
<td>8/6</td>
<td>11/3</td>
<td>s</td>
</tr>
<tr>
<td>14</td>
<td>22.1±1.4</td>
<td>10/4</td>
<td>8/6</td>
<td>11/3</td>
<td>l</td>
</tr>
<tr>
<td>s/s</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1/l</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>l/extra-l</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Subject characteristics of s group and l group.
were performed according to the manufacturer’s instructions. Forward and reverse primers were used to sequence the PCR products.

**Visceral stimulation**

Colorectal stimulation was performed using the same methods as previously described (Hamaguchi et al., 2004, Suzuki et al., in press). On the day before the experiment, subjects were given low-residue meals and their colorectum was cleansed. On the experimental day, a catheter with a barostat bag (700 ml in volume) was inserted into the rectum or the upper part of the descending colon by colonoscopy. Colorectal distention stimuli were provided with a computerized barostat equipment (Medtronic Synectics, Shoreview, MN, USA), which inflated the bag at a rate of 38 ml/s. First, each subject underwent a baseline PET scan without bag stimulation. Thereafter, the colorectum was stimulated with bag pressures of 0, 20 and 40 mm Hg for 80 s. The intensity of each stimulus was randomly chosen to avoid stimulation order effect, and the time interval between two stimuli was 15 min. After each stimulation, the subjects were asked to report the following 7 items of visceral perception or emotion: abdominal discomfort, abdominal distention, abdominal pain, urgency for defecation, perceived stress, sleepiness, and anxiety. Each sensation was evaluated on an ordinate scale from 0 (no sensation) to 10 (maximal sensation) (Hamaguchi et al., 2004, Kano et al., 2007).

**PET scan**

Scans of the distribution of $H_2^{15}$O were obtained using a SET-2400W PET scanner (Shimadzu, Japan) operated on a high sensitivity three-dimensional mode with an average axial resolution of 4.5 mm at maximum strength and sensitivity for a 20-cm cylindrical phantom of 48.6 kcps kBq$^{-1}$ ml$^{-1}$ (Fujwara et al., 1997, Kano et al., 2007). For each scan, a subject received approximately 5 mCi (185 MBq) of $H_2^{15}$O intravenously through the forearm vein and underwent colorectal distention during rCBF measurement. The radioactivity peak to the scan onset was about 10 s after the start of colorectal distention at which both the radioactivity peak and peak pressure of the bag simultaneously reached a plateau. The PET scanning room was darkened and the subjects, while awake, were instructed to keep their eyes closed for the whole period of scanning (70 s).

**Statistical analysis**

Statistical parametric mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, UK) was used for PET image realignment, normalization, smoothing, and to create statistical maps of significant rCBF changes (Friston et al., 1995a,b). All rCBF images were stereotaxically normalized into the standard space defined by Talairach and Tournoux (1988) using an rCBF template image supplied with SPM2. The normalized images were smoothed using a

\[ s(40\text{mmHg} - 0\text{mmHg}) > / (40\text{mmHg} - 0\text{mmHg}) \]

**Fig. 1.** Moderate colorectal distention in the s group significantly activated more the left anterior cingulate cortex than that in the l group. The image with 40 mm Hg was subtracted by that with 0 mm Hg. BA 32, x, y, z = −8, 40, −2, \(p < 0.0001\).

\[ s(40\text{mmHg} - 0\text{mmHg}) < / (40\text{mmHg} - 0\text{mmHg}) \]

**Fig. 2.** Moderate colorectal distention in the s group significantly activated more the right hippocampus than that in the l group. The image with 40 mm Hg was subtracted by that with 0 mm Hg. x, y, z = 32, −42, −4, \(p < 0.0001\).
12 × 12 × 12-mm Gaussian filter, and the rCBF values were expressed in ml dl⁻¹ min⁻¹, adjusted for individual global CBF values using ANCOVA, and scaled to a mean of 50. The contribution of each parameter of interest to changes in rCBF was estimated by SPM2 according to the general linear model at the voxel level. Estimates were made using linear compounds of contrasts, and the resulting set of voxel values constituted a parametric map for each contrast. To examine whether specific brain regions differed between the s group and the l group, we performed subtraction analysis between rCBF changes at stimulation. Brain regions with significant cluster level (p<0.05) and significant voxel level (T>4.0 and p<0.0001) were demonstrated.

Results

The brain image with 0 mm Hg was subtracted from the brain image with 40 mm Hg. This subtraction implies analysis of the brain area specific to the moderate colorectal stimulation. The s group showed a significantly larger increase in rCBF in the left ACC (BA 32, x, y, z = −8, 40, −2) by moderate colorectal distention than the l group (p<0.0001) (Fig. 1). The spatial distribution of the more activated area in the s group than in the l group was mainly the perigenual ACC including the supragenual ACC and subgenual ACC. The s group also showed a significantly larger increase in rCBF in the right hippocampus (x, y, z = 32, −42, −4) by mild colorectal distention than the l group (p<0.0001) (Fig. 2). The spatial distribution of the more activated area in the s group than in the l group included the parahippocampal cortex.

The brain image with 0 mm Hg was then subtracted from the brain image with 20 mm Hg. This subtraction implies analysis of the brain area specific to the mild colorectal stimulation. The increase in rCBF by mild colorectal distention in the s group was significantly larger in the left OFC (BA 47, x, y, z = −38, 24, −20) than that in the l group (p<0.0001) (Fig. 3). The more activated area in the s group than in the l group was located in the lateral margin of the OFC adjacent to the left temporal pole.

Table 2 shows a summary of the significantly more activated brain regions in response to colorectal stimulation in the s group than in the l group. There were no other regions which differentiate the brain response to colorectal distention between the s group and the l group.

We also analyzed the data after eliminating the 3 subjects with IBS in each group. The comparisons of the s and l groups remained statistically significant after excluding these subjects. Colorectal distention significantly and intensity dependently increased the ordinate scale of abdominal discomfort, abdominal distention, abdominal pain, urgency for defecation, perceived stress, and anxiety, and significantly reduced sleepiness in both groups (data not shown). However, the effect of 5-HTTLPR genotype on the changes in the ordinate scale was not significant.

Discussion

This is the first study to clarify that colorectal distention in individuals with the s/s genotype activates the ACC, hippocampus, and OFC more than in individuals with the l allele. The results of this study are in line with those of Hariri et al. (2002) and Pezawas et al. (2005). Hariri et al. (2002) reported that individuals with the s allele of 5-HTTLPR exhibit greater amygdala neuronal activity in response to fearful stimuli than individuals homozygous for the l allele. Pezawas et al. (2005) demonstrated tight coupling as a feedback circuit implicated in the extinction of negative affect by functional analysis of the ACC and amygdala during perceptual processing of fearful stimuli and relative uncoupling of this circuit in s allele carriers. Therefore, our present study, together with earlier studies, suggests that the s allele and l allele of 5-HTTLPR exhibit dysfunction of the prefrontal–limbic circuits in response to stimuli that usually evoke negative emotion.

The advantage of this study is that the stimulus we used (visceral stimulation) is known to directly activate the raphe nuclei in the brain.

Table 2
Summary of differential brain activation between s group and l group.

<table>
<thead>
<tr>
<th>Main effect</th>
<th>Region</th>
<th>Side</th>
<th>BA</th>
<th>Cluster</th>
<th>p</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>s−l (40 mm Hg−0 mm Hg)</td>
<td>Hippocampus</td>
<td>R</td>
<td>215</td>
<td></td>
<td>0.012</td>
<td>32</td>
<td>−42</td>
<td>−4</td>
<td>5.05</td>
</tr>
<tr>
<td>s−l (20 mm Hg−0 mm Hg)</td>
<td>Anterior cingulate cortex</td>
<td>L</td>
<td>32</td>
<td>183</td>
<td>0.019</td>
<td>−8</td>
<td>40</td>
<td>−2</td>
<td>4.91</td>
</tr>
<tr>
<td>s−s (20 mm Hg−0 mm Hg)</td>
<td>Orbitofrontal cortex</td>
<td>L</td>
<td>47</td>
<td>215</td>
<td>0.012</td>
<td>−38</td>
<td>24</td>
<td>−20</td>
<td>4.32</td>
</tr>
</tbody>
</table>

Side: R: right, L: left; BA: Brodmann’s area: regions with p<0.0001 were shown.
Neurons of the nucleus raphe magnus respond to colorectal distention by stimulating serotonin from nerve terminals and consequently a higher serotonin concentration in the blood. Therefore, in our study, serotonin neurons in the dorsal raphe nucleus were stimulated by colorectal distention, releasing serotonin from nerve terminals and consequently a higher serotonin concentration in the blood. This phenomenon results in a higher serotonin concentration in the synaptic cleft of the ACC, hippocampus, and OFC in individuals with the s allele. Serotonin neurons stimulate the ACC, hippocampus, and OFC through presynaptic nerve terminals, excite postsynaptic neurons, and produce a paradoxical increase in neuronal discharge in response to depolarizing input. However, serotonin often produces complex and variable responses, leading to the hyperpolarizing response and serotonin receptors. Different receptors, including serotonin-dependent K-conductance, lead to neuronal depolarization and excitation, and serotonergic neurotransmission. The perigenual ACC is divided into two parts, one of which is associated with negative emotion and the other with positive emotion. The perigenual ACC is related to negative emotion and conflict monitoring (Ressler and Mayberg, 2007). The perigenual ACC is divided into two parts, namely, the supragenual ACC and subgenual ACC. The function of the supragenual ACC negatively correlates with amygdala activity, while that of the subgenual ACC positively correlates with amygdala function (Pezawas et al., 2005). 5-HTTLPR s allele carriers show less coupling between the amygdala and the perigenual ACC than l/l individuals, particularly in the subgenual ACC (Shah et al., 2009). The influence of 5-HTTLPR on coupling between the ACC and amygdala during visceral perception processing warrants future study. The hippocampus is the key region for explicit and implicit memory. It is also implicated in emotion and emotion-related learning. Distinct areas of the OFC were shown to be activated by monetary rewards and punishments. Moreover, these areas are reported to be correlated with the magnitude of brain activation and the magnitude of rewards and punishments received. Further, medial OFC activity is related to monitoring the reward value of many different reinforcers, whereas lateral OFC activity is related to the evaluation of punishments which may lead to a change in ongoing behavior (Kringelbach and Rolls, 2004). A posterior—anterior distinction exists with more complex or abstract reinforcers (such as monetary gain and loss) represented more anteriorly in the OFC than simpler reinforcers such as taste or pain. Our data showing more activation of the lateral and posterior OFCs suggest that individuals with the s/s genotype tend to evaluate mild visceral activation as a punishment marker. There was no significant association between 5-HTTLPR genotype and self-reported distress and discomfort. We believe this finding to be reasonable because quantification of subjective feeling is relatively insensitive compared with neural or chemical changes (Hamaguchi et al., 2004, Kano et al., 2007, Suzuki et al., in press). The brain processes unconscious signals on a moment-to-moment basis and only a part of them is processed consciously. This finding also suggests that 5-HTTLPR genotype first influences rCBF as the endophenotype. We assume that either a larger number of subjects or long-term analysis of subjective feeling in response to colorectal distention is necessary to detect the effect of 5-HTTLPR genotype on phenotype (negative emotion). The limitations of the present study are as follows. First, there is a difference in treating heterozygosity of 5-HTTLPR between our study and earlier well-known studies. Earlier studies compared the l/l genotype versus the s/l and s/s genotypes based on the hypothesis that the s allele is dominant (Hariri et al., 2002, Pezawas et al., 2005). We compared the s/s genotype versus the s allele because the s allele is more frequent in the Asian population (Mizuno et al., 2006). In a Caucasian sample, the l allele is reported to be dominant (Hanna et al., 1998, Du et al., 1999, Williams et al., 2001). If 5-HTTLPR truly affects emotional sensitivity to stimuli, the l or s allele will be responsible for emotion independent of race. There are some reports showing that patterns of linkage disequilibrium between 5-HTTLPR and other sites on the 5-HT gene vary considerably across racial (including European, African, and Japanese) groups (Gelernter et al., 1997) and that there are race and sex differences in the association between 5-HTTLPR genotype and personality traits associated with negative emotion (Gelernter et al., 1998). It is possible that race differences exist with respect to the transcriptional efficiency of the s versus l alleles. Because our sample was composed mainly of men, it is impossible to evaluate the sex modulation of 5-HTTLPR effects on brain activation. In previous larger sample studies, however, it should be noted that Caucasian (Lesch et al., 1996, Gelernter et al., 1998) and Japanese (Mizuno et al., 2006) men with more s alleles consistently showed increased anxiety levels. Further studies will be needed to determine whether the effects of 5-HTTLPR on brain activation relate to other racial groups. Second, we did not assess the single nucleotide polymorphism of an A → G substitution which is located at nucleotide 6 within the first of two extra 22-base pair repeats that characterize the l allele located 1629 nt 5′ of exon 1 of 5-HT (Hu et al., 2006). The l allele has greater transcriptional activity than the l allele which has transcriptional activity similar to the s allele. We cannot completely exclude the possibility that this 5-HTTLPR triallelic may have influenced our results to some extent. This possibility should be explored in future studies. Third, our sample contained 3 subjects with IBS among the 14 subjects in each group, which is similar to the prevalence of IBS in the general population, and analysis eliminating the IBS subjects resulted in the same results. Moreover, the aim of the present study was to ascertain the genetic effects on the brain processing of visceral activation. Possible differential influence of 5-HTTLPR between controls and IBS should be examined in future studies with a greater number of subjects. Fourth, the descending colon and rectum were stimulated. However, the numbers of stimulated site were not statistically different between the s group.
and the I group. Moreover, the activated brain regions are not discriminatory parts along the somatotopic order of the descending colon and rectum. More samples of the I/I genotype and the same site of stimulation should be used in future studies. Despite these limitations, the present study clearly demonstrated the effect of 5-HTTLPR on interoceptive emotional processing.

In conclusion, the present data suggest that individuals with a weak function of serotonin transporter respond to gut signals more in emotion-regulating brain regions. Functional gene polymorphism may partially predict the individual effects of long-lasting neural processing from visceral organs.

Acknowledgments

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