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Dose dependency of brain histamine H1 receptor occupancy following oral administration of cetirizine hydrochloride measured using PET with [^{11}C]doxepin

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Aims The strength of sedation due to antihistamines can be evaluated using positron emission tomography (PET). The purpose of the present study is to measure histamine H_1 receptor (H_1R) occupancy following oral administration of cetirizine (10 and 20 mg) in order to examine dose dependency.
Methods Fifteen healthy male volunteers (age range, 20–35 years) were divided into 3 subgroups and were studied following single oral administration of cetirizine at 10 mg ($n = 5$) and 20 mg ($n = 5$) or hydroxyzine at 30 mg ($n = 5$) using PET with ^{11}C-doxepin. Each subject was scanned also following the administration of placebo. Binding potential and H_1RO values were calculated in the prefrontal and anterior cingulate cortices. Subjective sleepiness was also measured, and the correlation to H_1RO was examined for each antihistamine.
Results The averaged H_1ROs of cetirizine 10 mg, 20 mg, and hydroxyzine 30 mg in the prefrontal and cingulate cortices was 12.6%, 25.2%, and 67.6%, respectively. The H_1RO of hydroxyzine 30 mg correlated well with subjective sleepiness ($p < 0.001$); however, those of cetirizine 10 and 20 mg showed no correlation with subjective sleepiness.
Conclusion It was demonstrated that the brain penetration of orally administered cetirizine was dose-dependent. Cetirizine 10 mg, with its low H_1RO and thus minimal sedation, could be more safely used than cetirizine 20 mg for the treatment of various allergic disorders.

KEY WORDS — cetirizine; hydroxyzine; histamine H_1 receptor (H_1R); histamine H_1 receptor occupancy (H_1RO); positron emission tomography (PET); binding potential; sedation

INTRODUCTION

Histamine H_1 receptor (H_1R) antagonists commonly known as antihistamines are often used for the treatment of allergic disorders such as seasonal rhinitis. Antihistamines act mainly on the peripheral tissues but can also induce sedation as a central side effect. This undesirable side effect is caused by blockade of nerve transmission in the histaminergic neuronal system. This system projects from the tuberomammillary nucleus in the posterior hypothalamus to almost all cortical areas (Casale et al., 2003; Haas and Panula, 2003; Holgate et al., 2003). First-generation (sedative) antihistamines that can easily penetrate the blood-brain barrier (BBB), such as d-chlorpheniramine and hydroxyzine, tend to occupy a large proportion of post-synaptic H_1Rs (more than 50%) (Yanai et al., 1995a; Yanai et al., 1995b; Yanai et al., 1999; Okamura et al., 2000; Tagawa et al., 2001; Van Hoecke et al., 2007). Mildly-sedative antihistamines, such as cetirizine and terfenadine, slightly penetrate the BBB and mildly occupy H_1Rs in the brain (usually not more than 20% or so). Moreover, they tend to induce slight sedation at low or recommended doses, but cause dose-related cognitive impairment at higher doses. Non-sedative antihistamines (e.g., fexofenadine), which have recently been introduced as an additional subcategory, can hardly penetrate the BBB and sparingly occupy H_1Rs. Since they do not penetrate the BBB easily, they induce no sedation even at exceeded doses (Hindmarch et al., 2002; Casale et al., 2003; Holgate et al., 2003; Van Hoecke et al., 2007). We previously demonstrated the difference in BBB

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permeability between mildly-sedative and non-sedative antihistamines using positron emission tomography (PET) and [^{11}C]doxepin following oral administration of double doses of cetirizine (20 mg) and fexofenadine (120 mg) (Tashiro et al., 2004). Thus, variation in cerebral H_1R occupancy (H_1RO) of antihistamines can be evaluated in terms of "BBB permeability" using PET and [^{11}C]doxepin.

It is of great social importance to note that users of mildly-sedative antihistamines tend to be less cautious and might take these drugs at double or triple doses when the desired effects are not achieved by the recommended doses even while driving a car or operating potentially dangerous machinery (Casale et al., 2003; Haas and Panula, 2003; Holgate et al., 2003). It is therefore important to examine the dose dependency of mildly-sedative antihistamines since no study has been available to date regarding the comparison of H_1ROs following treatment with these antihistamines at different doses. The primary aim of the present study is to compare the H_1ROs of cetirizine at 10 and 20 mg using PET, as well as to examine such cetirizine H_1ROs against that of hydroxyzine at 30 mg, a typical sedative antihistamine.

METHODS

The present study was approved by the Committee on Clinical Investigation of the Tohoku University Graduate School of Medicine and by the Institutional Review Committee of the Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan, and was performed in accordance with the policy of the declaration of Helsinki.

Subjects and study design

Fifteen male Japanese volunteers (age range, 20–35 years), recruited through an advertisement as study subjects, were provided with a clear description of the study, and their written informed consents were obtained. All the subjects were in good health with no clinical history of major physical or mental illnesses, and were also not receiving any concomitant medication likely to interfere with the study results. There were no abusers of alcohol, caffeine, or nicotine. Alcohol, nicotine, caffeine, grapefruit, and grapefruit juice were forbidden during the study period, and food intake was controlled on the test day and the day before PET measurement. The volunteers were requested to finish a light meal at least 3 h before the start of the study.

Out of the 15 subjects, each of five subjects was administered cetirizine at 10 mg (CET10 group: mean age +/- S.D. = 21.6 +/− 1.5 y.o.; mean body weight [BW] = 60.8 +/− 7.1 kg), cetirizine at 20 mg (CET20 group: mean age +/- S.D. = 23.2 +/− 1.1 y.o.; mean BW = 60.8 +/− 5.4 kg), and hydroxyzine at 30 mg (HYD group: mean age +/- S.D. = 23.2 +/− 0.8 y.o.; mean BW = 63.6 +/− 8.6 kg). Each subject underwent PET measurements after single oral administration of one of the above antihistamines or placebo (i.e., lactobacteria preparation, 6 mg), with minimum washout intervals of 7 days between treatments. Active and placebo conditions were cross-randomized in the present study. Lactobacteria preparation has been widely used as placebo in Japan, and has shown no statistical difference between pre- and post-administration in our previous cognitive studies (Okamura et al., 2000; Tagawa et al., 2002; Tashiro et al., 2004).

Measurement of subjective sleepiness

In each subject, subjective sleepiness was measured using the line analogue rating scale (LARS) (Parkin et al., 1998; Shamsi et al., 2001) at pre-administration and 0.5, 1, 1.5, 2, 2.5, and 3 h post-administration of each antihistamine or placebo. For each antihistamine condition, the measured subjective sleepiness was compared with that following placebo administration (Figure 1).

PET tracer and image acquisition

[^{11}C]doxepin was prepared by [^{11}C]methylation of desmethyl doxepin with [^{11}C]methyl triflate, as described previously (Iwata et al., 2001). The radiochemical purity of [^{11}C]doxepin was more than 99%, and its specific radioactivity at the time of injection was 64.9 +/− 45.3 GBq/μmol (1.75 +/− 1.23 Ci/μmol). [^{11}C]doxepin-containing saline solution was intravenously injected to each subject at 90 min after oral administration of the antihistamines, which was nearly similar to the known T_{max} of each antihistamine used: 2.1 +/−0.4 h for hydroxyzine in healthy Caucasoids, and 1.4 +/− 0.5 for CET 10 mg and 1.5 +/− 0.4 for 20 mg in Japanese volunteers (Simons et al., 1984; Lefebvre et al., 1988; Sasa et al., 1995; Tashiro et al., 2004). The injected dose and cold mass of [^{11}C]doxepin were 143.2 +/− 40.8 MBq (3.87 +/− 1.10 mCi), and 3.65 +/− 2.80 nmol, respectively.

Shortly before [^{11}C]doxepin injection, the subjects were positioned on the coach of the PET scanner so that

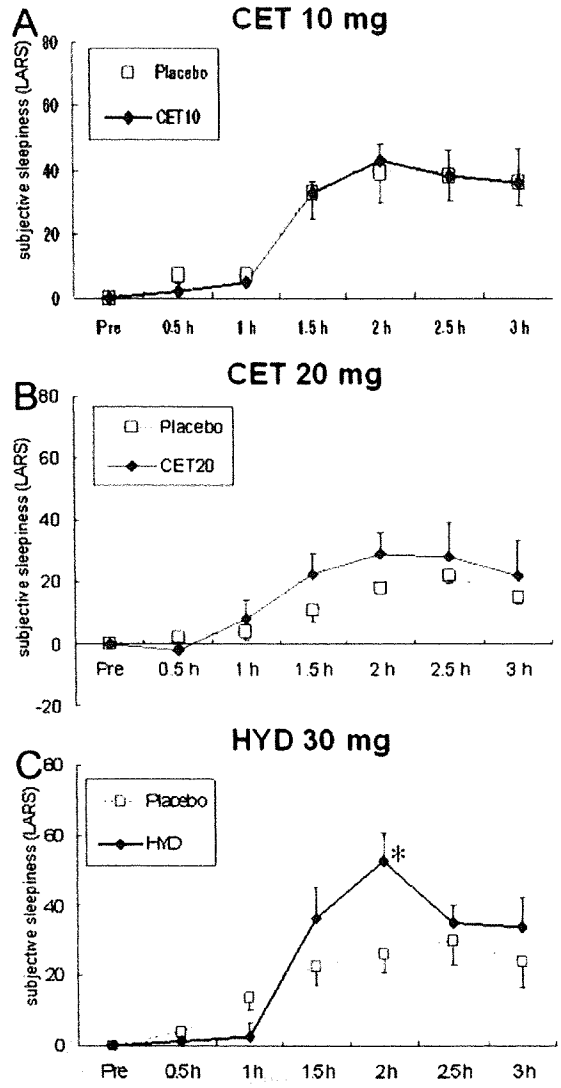

Figure 1. Results of measurements of subjective sleepiness following oral administration of cetirizine (10 and 20 mg), and hydroxyzine (30 mg). Each graph indicates the time-course of subjective sleepiness measured using the line analogue rating scale (LARS) at pre-administration and 0.5, 1, 1.5, 2, 2.5, and 3 h post-administration. Following cetirizine (10 mg) administration, there was no significant difference compared with following placebo administration (A). Following cetirizine (20 mg) administration, there was a trend for increased sleepiness, but a significant difference was not shown relative to the placebo condition (B). Following hydroxyzine (30 mg) administration, there was a significant increase in sleepiness compared with the placebo condition (C). Abbreviations: Pre = pre-administration, CET10 = cetirizine 10 mg, CET20 = cetirizine 20 mg, HYD = hydroxyzine

the transaxial slices were parallel to the orbitomeatal line. Subjects taking cetirizine at 10 and 20 mg were scanned using SET-2400W (Shimadzu Co., Kyoto, Japan), and those taking hydroxyzine at 30 mg were scanned using ECAT PT931 (CTI, Inc., Knoxville, TN, USA). Further details regarding these scanners were described in our previous reports (Fujiwara et al., 1997; Tashiro et al., 2004). Following transmission scan using the $^{68}Ge/^{68}Ga$ line source for tissue attenuation correction, the subjects were then scanned to detect emission of high-energy photons (511 keV) (emission scan). After tissue attenuation correction and reconstruction with a filtered back-projection algorithm, the brain images were processed by applying graphical analysis to obtain binding potential (BP) images (Logan et al., 1990; Logan et al., 1996) using the time–activity curve in the cerebellum based on region of interest (ROI) analysis. This method was previously validated and described in detail (Suzuki et al., 2005). Finally, H_1RO was calculated based on the BP values of the frontal cortex and cingulate gyrus, where the H_1R density was the highest and the most suitable for H_1RO calculation. The H_1ROs of antihistamines were calculated based on the following equation: $H_1RO = [(BP \text{ with placebo} - BP \text{ with given antihistamine}) / BP \text{ with placebo}] \times 100$.

Statistical analysis. Differences in H_1ROs between cetirizine (10 and 20 mg) and hydroxyzine (30 mg) were examined using one-way ANOVA with Bonferroni correction for multiple comparisons. The relationship between plasma drug concentration and H_1RO was examined using Pearson's correlation test. A probability of $p < 0.05$ was considered statistically significant. All statistical examinations were performed using SPSS for Windows 15.0 (Japanese version). For correlation analysis between H_1RO and subjective sleepiness, we have calculated the "LARS_AUC ratio" by taking the ratio of AUC curves of subjective sleepiness (LARS) following an antihistamine treatment to that following placebo treatment, in order to normalize inter-individual differences of subjective sleepiness. And correlation was examined between H_1RO and subjective sleepiness.

RESULTS

Subjective sleepiness

Results of subjective sleepiness measurements using LARS are shown in Figure 1. Subjective sleepiness following cetirizine 10 mg administration was not significantly different compared with that following placebo administration (Figure 1A). Following cetirizine 20 mg administration, a trend for increased sleepiness was observed, but this increase showed no

Table 1. Binding potential and histamine H_1 receptor occupancy following administration of antihistamines and placebo

Drug and Region	BP (S.E.M.)	BP_{Pla} (S.E.M.)	H_1RO [%](S.E.M.)
Hydroxyzine (30 mg)	BP_{HYD}	BP_{Pla}	H_1RO_{HYD}
frontal	0.15 (0.06)	0.53 (0.07)	64.4 (9.1)
cingulate	0.24 (0.03)	0.67 (0.02)	70.7 (5.8)
Cetirizine (20 mg)	BP_{CET20}	BP_{Pla}	H_1RO_{CET20}
frontal	0.44 (0.09)	0.62 (0.11)	25.5 (9.5)
cingulate	0.50 (0.04)	0.66 (0.05)	24.8 (6.5)
Cetirizine (10 mg)	BP_{CET10}	BP_{Pla}	H_1RO_{CET10}
frontal	0.54 (0.04)	0.62 (0.05)	11.6 (3.3)
cingulate	0.68 (0.03)	0.78 (0.02)	13.6 (3.4)

significant difference compared with the placebo condition (Figure 1B). After hydroxyzine 30 mg administration, a significant increase in sleepiness was observed compared with the placebo condition (Figure 1C).

ROI-based comparison of BP and H_1RO

BP values in H_1R-rich regions such as the frontal and cingulate cortices were evaluated based on ROI analysis (Table 1 and Figure 2). BP values following treatment with cetirizine 10 mg were only slightly lower than that following placebo treatment in the same subjects. However, BP values following treatment with hydroxyzine 30 mg were considerably low compared with those following placebo treatments. BP values after treatment with cetirizine 20 mg were between those following treatments with cetirizine 10 mg and hydroxyzine 30 mg (Table 1).

H_1ROs following treatment with cetirizine (10 and 20 mg) and hydroxyzine (30 mg) were also calculated using the BP following antihistamine treatment in each subject and utilizing the BP data following placebo treatment in each subject as baseline (0%) (Table 1, Figure 2). The mean H_1ROs of the frontal and cingulate cortices following treatment with cetirizine 10 mg were 11.6 and 13.6%, respectively (average, 12.6%). Those following treatment with cetirizine 20 mg were 25.5 and 24.8%, respectively (average, 25.2%). Those following treatment with hydroxyzine 30 mg were 64.4 and 70.7%, respectively (average, 67.6%). These results show that H_1RO following treatment with hydroxyzine is substantially higher than that following treatment with cetirizine (Table 1, Figure 2). The differences in both the cetirizine groups to the hydroxyzine group were statistically significant (Figure 2).

As for the correlation between H_1RO and subjective sleepiness, the significant positive correlation was observed with hydroxyzine in the frontal cortex ($r=0.91$, $p=0.034$) but not in the cingulate cortex ($r=0.76$, $p=0.14$), respectively (Figure 3). A trend for positive correlation was observed with cetirizine 20 mg, although the correlation was not significant in neither the cingulate ($r=0.68$, $p=0.21$) nor frontal ($r=-0.74$, $p=0.15$) (Figure 3). As for cetirizine 10 mg, H_1RO and subjective sleepiness were inconsistent, demonstrating trends for positive correlation in the cingulate cortex ($r=0.47$, $p=0.43$) and negative

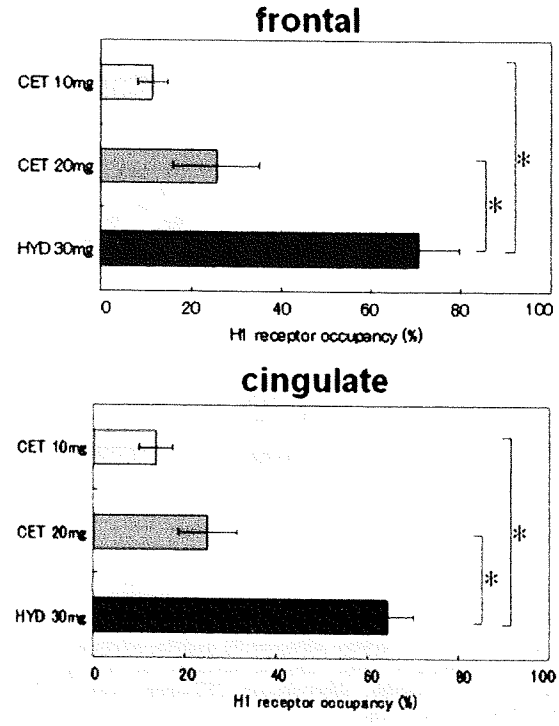

Figure 2. Histamine H_1 receptor occupancy (H_1RO) in the cingulate and frontal cortices. ROI measurements were performed in the anterior cingulate and frontal cortices following oral administration of cetirizine (10 and 20 mg) and hydroxyzine (30 mg). H_1RO due to these antihistamines are shown, taking H_1RO by those under the placebo condition as 0%. H_1RO of hydroxyzine following administration was significantly higher than those of the other antihistamines. * $p<0.001$, ANOVA followed by the Bonferroni test for multiple comparison. Error bars represent inter-individual variability (S.E.M.). Abbreviations: CET10mg = cetirizine 10 mg, CET20 mg = cetirizine 20 mg, HYD30 mg = hydroxyzine 30 mg

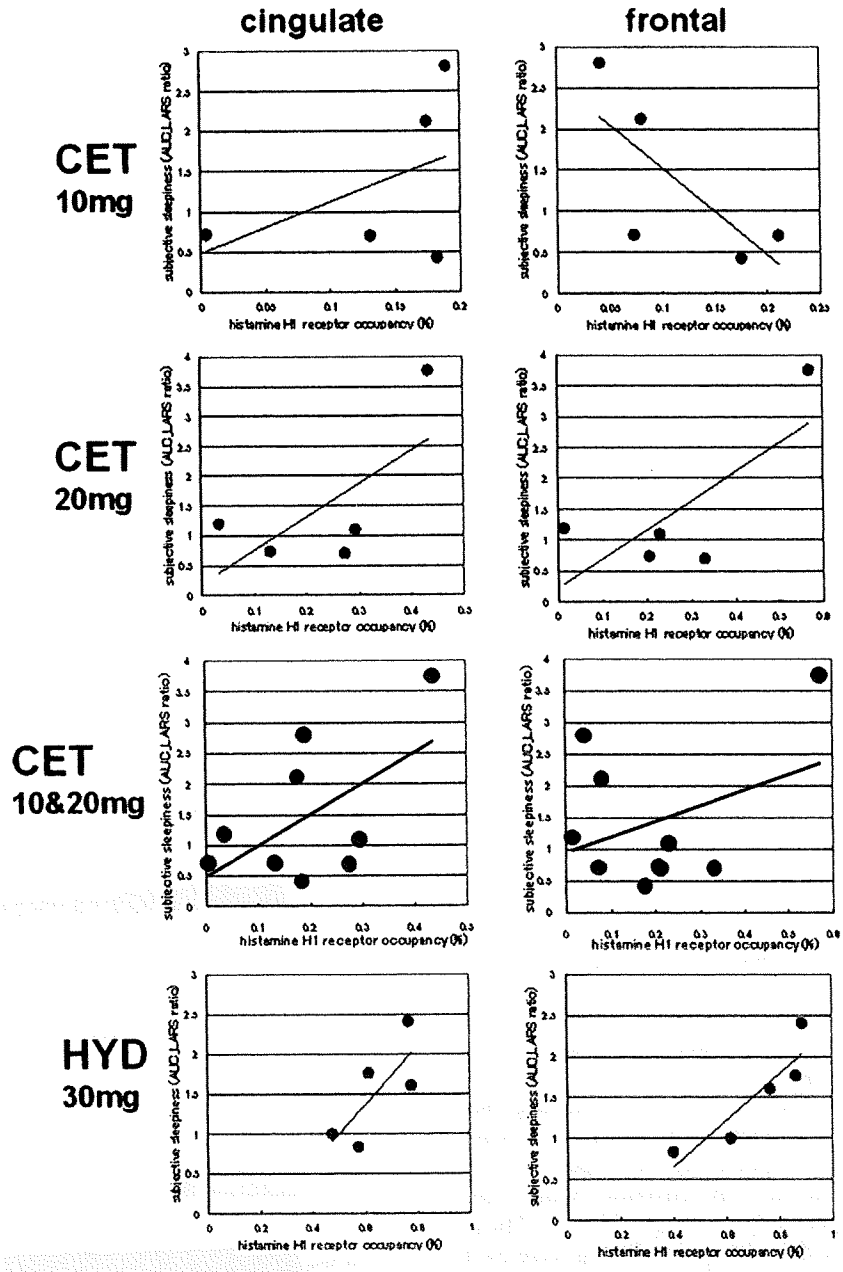

Figure 3. Correlation between histamine H1 receptor occupancy (H_1RO) and subjective sleepiness in the cingulate and frontal cortices. Subjective sleepiness is indicated as the ratio of area under the curves for the 3 h-long follow-up data of line analogue rating scale (LARS) following oral administration of each antihistamine and placebo. Abbreviations: CET10mg = cetirizine 10 mg, CET20mg = cetirizine 20 mg, CET10&20 mg = cetirizine 10 and 20 mg, HYD 30mg = hydroxyzine 30 mg

correlation in the frontal cortex ($r = -0.73$, $p = 0.16$), though both were insignificant (Figure 3). When cetirizine 10 and 20 mg data were plotted together, a trend for positive correlation was observed in the cingulate ($r = 0.58$, $p = 0.08$) but not in the frontal regions ($r = 0.36$, $p = 0.30$) (Figure 3).

DISCUSSION

In the present study, the H_1RO of cetirizine, a mildly-sedative antihistamine, was compared between two doses of 10 and 20 mg in a single-blinded placebo-controlled study design. Moreover, the H_1RO of

hydroxyzine 30 mg, a typical sedative antihistamine, was also calculated. In previous research, we calculated the H_1RO of oral cetirizine 20 mg; however, the investigation was not a placebo-controlled study. This means that the control data used for calculating H_1ROs were obtained from different subjects with the aim of reducing radiation exposure to subjects (Tashiro et al., 2004). In addition, the H_1RO of hydroxyzine was not measured in that previous study. Thus, an additional aim of the present study was to measure the H_1RO of hydroxyzine at 30 mg. The placebo-controlled study design required at least two scans for each subject and for each drug, and the use of the three-dimensional (3D) data acquisition mode enabled the reduction of radiation exposure (mean +/- S.D.: 1.98 +/− 0.57 mSv), that is, considerably smaller than that in our previous study using the 2D data acquisition mode (average, 4.31 mSv) (Tashiro et al., 2004). Therefore, the 3D data acquisition mode is suitable for conducting placebo-controlled PET clinical trials.

In the present study, we found that the baseline BP under the placebo condition showed a certain inter-individual variation (the mean values under the placebo condition for the subgroups of cetirizine 10 and 20 mg and hydroxyzine 30 mg were 0.62 +/− 0.05, 0.62 +/ − 0.11, and 0.53 +/− 0.07, respectively)(Table 1). This result suggests the use of a placebo-controlled study design could minimize the effect of inter-individual variation, although the H_1RO of cetirizine 20 mg in this placebo-controlled study (mean value of frontal and cingulate cortices, 25.2%) was slightly different from that obtained in our previous study (mean value of frontal and cingulate cortices. 28.9%) (Tashiro et al., 2004).

It has been known that sedative antihistamines, such as hydroxyzine, ketotifen, diphenhydramine, and d-chlorpheniramine, occupy more than 50% of available H_1Rs, resulting in high prevalence of sleepiness and cognitive decline (Yanai et al., 1995a; Okamura et al., 2000; Tagawa et al., 2001; Tashiro et al., 2006; Van Hoecke et al., 2007; Tashiro et al., 2008). Hydroxyzine is a typical sedative antihistamine that induces psychomotor impairment even at recommended doses (20–30 mg), and it has been used as a positive control in many studies (Gengo et al., 1987; Gengo and Gabos, 1987; Walsh et al., 1992; Lee and Maibach, 2001; Van Hoecke et al., 2007). Cetirizine, also used in this study, is the main metabolite of hydroxyzine, and the conversion from hydroxyzine to cetirizine is mediated by alcohol dehydrogenase (Whomsley et al., 2005). In the present study, subjective sleepiness in the hydroxyzine group was significantly increased compared with the placebo condition, while the cetirizine subgroups did not show significant difference from the placebo conditions (Figure 1). In addition, H_1ROs following hydroxyzine treatment showed a significant difference relative to those following cetirizine treatment (Figure 2).

Mildly-sedative antihistamines, including cetirizine and loratadine, are regarded as less impairing and sedating than sedative antihistamines. For example, cetirizine at the recommended doses of 5–10 mg has been evaluated as being either non-sedating (Gengo et al., 1987; Gengo et al., 1990; Walsh et al., 1992; Patat et al., 1995; Hindmarch et al., 2001; Shamsi et al., 2001; Curran et al., 2004; Van Hoecke et al., 2007; Takahashi et al., 2008) or mildly sedating (Ramaekers et al., 1992; Bonifazi et al., 1995; Vermeeren et al., 2002). These results from the use of cetirizine are variable; at higher than the recommended doses (20 mg), the agent has been reported to produce significant drowsiness (Gengo and Gabos, 1987) and impairment in a selected task (Gengo et al., 1990) in some studies or no cognitive impairment (Gengo et al., 1987; Gengo and Gabos, 1987) in other investigations. In a recent meta-analysis (Hindmarch and Shamsi, 1999; Shamsi and Hindmarch, 2000), the proportional impairment ratios (PIRs) based on objective measurements were 0.18 and 2.25 for cetirizine and hydroxyzine, respectively. The PIRs based on subjective measures were 0.33 and 2.57 for cetirizine and hydroxyzine, respectively (Hindmarch and Shamsi, 1999), where a smaller PIR corresponds to a weaker sedative effect.

Therefore, it has been thought that second generation antihistamines are less impairing for use in day-to-day activities (Mattila and Paakkari, 1999; Tashiro et al., 2004; Theunissen et al., 2004). However, the strength of sedation seems to vary among users and further investigations have demonstrated that not all second generation antihistamines manifest similar "non-sedative" profiles. Recently, second generation antihistamines have been further classified into the following two subgroups (Casale et al., 2003; Holgate et al., 2003): those inducing slight sedation at low doses, but causing dose-related cognitive impairment at higher doses ("mildly-sedative" antihistamines, e.g., cetirizine), and those inducing no sedation even at exceeded doses ("non-sedative" antihistamines, e.g., fexofenadine) (Tashiro et al., 2004). Based on this classification, we previously compared the BBB permeability of cetirizine 20 mg and fexofenadine 120 mg (both doses were double the standard oral doses

in Japan) in terms of H_1ROs. The results showed that the H_1ROs of both drugs were 26 and 0%, respectively (Tashiro et al., 2004). The H_1RO of 26% (mean value for the whole brain) was relatively high for a mildly-sedative antihistamine, suggesting that cetirizine might show dose-related brain penetration. This has been the rationale for conducting the present study in order to investigate whether dose-related BBB penetration is present or not. Examining the dose dependency of mildly-sedative antihistamines is also of great social importance because of overcompliance as mentioned in the introduction section. Comparison of H_1ROs following the oral administration of cetirizine 10 and 20 mg indicated clear dose-dependency in H_1ROs (Table 1 and Figure 2), although the difference was not statistically significant (Figure 2).

Variation in the BBB permeability among different antihistamines can be explained by various factors such as lipophilicity, molecular size, and different actions of drug transporters including a P-glycoprotein (P-gp). This is an efflux pump expressed in capillary endothelial cells in the BBB (Tashiro et al., 2006). Many sedative antihistamines are often lipophilic and can be absorbed in full amount in the gut, and they can freely diffuse into the brain space. In the case of mildly-sedative antihistamines with reduced lipophilicity, both gut absorption and brain penetration are limited. For fexofenadine, a substrate of P-gp, both gut absorption and BBB permeability are highly reduced because of its low membrane permeability and high action of P-gp. For cetirizine, also a substrate of P-gp but probably to a lesser extent than fexofenadine, will allow a certain amount of BBB penetration (Chen et al., 2003; Molimard et al., 2004). Our recent study demonstrated that bepotastine 10 mg, a new mildly-sedative antihistamine produced in Japan, has a similar structure to that of cetirizine and its H_1RO is similar to that of cetirizine 10 mg (mean value of frontal and cingulate: cortices,12.1%) (Tashiro et al., 2008). It is interesting to mention that bepotastine's chemical structure resembles that of cetirizine and its membrane permeability is greater than that of fexofenadine (Ohashi et al., 2006).

In our previous healthy volunteer study ($n = 10$)(Tashiro et al., 2004), the plasma concentrations of hydroxyzine and cetirizine (a main metabolite) following oral administration (120 min post-administration) of hydroxyzine 30 mg was 20.0 +/− 9.3 ng/ml and 146.3 +/− 50.3 ng/ml, respectively, although these results were not presented in the paper. In addition, the plasma cetirizine concentration following cetirizine treatment (20 mg) was 489.0 +/− 118.8 ng/ml. These pharmaco-kinetic data may suggest that a large proportion of hydroxyzine molecules rapidly distributed from the plasma into the tissue compartment and relatively small part of hydroxyzine molecules is rapidly metabolized into cetirizine. And according to Simons and colleagues, the elimination half lives do not differ largely between hydroxyzine (29.3 +/− 10.1 h) and cetirizine (24.8 +/− 7.7 h)(Simons et al., 2008). It seems that the subjective sedation is not associated with the plasma cetirizine concentration, but is associated with the brain distribution (penetration) of hydroxyzine measured as H_1RO.

Interestingly, a significant correlation between H_1RO and subjective sleepiness was observed following treatment with hydroxyzine 30 mg, but not following the treatment with cetirizine (Figure 3). This result suggests that subjective sleepiness is not reliable for evaluating the level of sedation particularly for mildly-sedative antihistamines. Thus, measurement of H_1RO using PET seems to be promising as recommended by the consensus group on new generation antihistamines (CONGA) (Holgate et al., 2003). CONGA is responsible for summarizing the core measures regarding the evaluation of the sedative profiles of new generation antihistamines (Holgate et al., 2003).

Here, we should discuss the limitations of the present study. First, we did not find a good correlation between subjective sleepiness and H_1RO. This would be partly because of inter-individual differences in drug responses. Considering variation in the results of previous cognitive studies on cetirizine (Gengo and Gabos, 1987; Gengo et al., 1990; Ramaekers et al., 1992; Bonifazi et al., 1995; Vermeeren et al., 2002), cetirizine is possibly an agent with relatively large inter-individual difference in its sedation. For the future replication to evaluate dose dependency, it would be better to scan each subject under three conditions of CET10, 20 mg and placebo using the same PET scanner. Different scanners were used for different antihistamines in the present study, though both scans were respectively compared to the placebo data obtained by the same scanner. In the second point, we did not measure the plasma drug concentration and were not able to examine the direct relationship between plasma drug concentration and H_1RO. Future study should clarify this relationship as well.

In conclusion, we examined the H_1RO of cetirizine at different oral doses of 10 and 20 mg, and compared the results with those from the oral administration of hydroxyzine 30 mg. Cetirizine 10 mg occupied

approximately 13% of available H_1Rs in the frontal brain (frontal and cingulate cortices), while cetirizine 20 mg occupied approximately 25% of H_1Rs, confirming that brain penetration of mildly-sedative antihistamines tends to be dose-dependent. In addition, it is noteworthy for users to know that oral administration of cetirizine 10 mg could be more safely used for the treatment of allergic disorders, while an increased dose (20 mg or more) could result in mild sedation.

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Chapter IV

Is Colonic Hypersensitivity Really a Biological Marker of Irritable Bowel Syndrome (IBS)? -A Role of Visceral Sensitivity on Pathophysiology of IBS.

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Introduction

Irritable bowel syndrome (IBS) is common and has a great impact on quality of life of the patients and medical/social economy [1], yet the mechanisms by which symptoms arise are poorly understood. Chronic and/or recurrent abdominal pain/discomfort associated with abnormal bowel habits is a main symptom of IBS [1, 2]. Current Rome III diagnostic criteria for functional gastrointestinal disorders are based on only clinical GI symptoms and symptom frequency [3]. Although abnormal gastrointestinal motility has been considered to be strongly associated with major symptoms of IBS for years, recent studies revealed some disappointing findings in terms of purely motility disorders [4]. Currently, visceral hypersensitivity is the leading hypothesis to explain the major pathophysiology of IBS and other functional gastrointestinal disorders [5].

In 1973, Ritchie [6] first reported that IBS patients showed more sensitive to intraluminal balloon distention of the colon than normal subjects. A barostat technique, in which operating pressure and volume in the bag inserted in the gut are controlled and recorded by a computer

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via an air inflation device, was developed approximately two decades ago [7, 8] and is widely used to determine visceral hypersensitivity for now. Using this technique, Whitehead et al. [7], Mertz et al. [9] and others [10] confirmed that majority of IBS patients have lower pain thresholds in response to colonic or rectal distention. Mertz et al. [9] proposed that altered visceral perception in the rectum is a biological marker of patients with IBS. Underlying visceral hypersensitivity in most of IBS patients was observed as allodynia (decreased nociceptive threshold) and/or hyperalgesia (increased nociceptive response). Bouin et al. [11] found that pain threshold to the rectal distention was highly specific inferior to 28 mmHg and was rare superior to 40 mmHg. Furthermore, recent studies [12, 13] using a barostat technique demonstrated that there was no difference in pain perception threshold to intraluminal distention between subtypes of bowel movement in IBS patients.

However, little is known about precise mechanism of visceral hypersensitivity and relationships between clinical symptoms and visceral sensitivity in patients with IBS. In the current article, possible mechanisms of abnormal visceral perception in IBS are discussed, focusing on the brain-gut interaction.

Possible Mechanism of Visceral Hypersensitivity in IBS

Visceral sensory signals are transmitted from the gut via afferent nerve fibers traveling through the spinal cord to the brain. Brain response to some stimulus in the peripheral organs is measured by several imaging techniques (e.g. positron emission tomography, PET or functional magnetic resonance imaging, fMRI). Human brain imaging studies suggested that IBS patients may have altered central activations (e.g. anterior cingulate cortex, ACC) during painful rectal distention compared with healthy subjects [14-17]. The enhanced central response could be caused by an increased signal and/or the signal amplification from the gut to the brain via the spinal cord and brainstem. In addition, disturbance in the descending pain inhibitory system on the brain-gut link could give rise to visceral hypersensitivity.

Patients with IBS showed more enhanced perception in the gut to psychological or physiological stress condition [18] or attention/hypervigilance itself to the aversive stimulus [19]. Anticipation to rectal painful distention alone enhanced the similar brain areas with response to actual rectal stimulation [20]. On the contrary, placebo administration [21] or distraction to aversive stimulus [22] could cause decrease in visceral perception.

On the other hand, previous findings on the modulation of pain sensitivity in the colon support some mechanisms of peripheral sensitization in IBS: (1) An abnormal colo-colic reflex in the forms of exaggerated motility was demonstrated after repetitive nonpainful distentions of the sigmoid colon in patients with IBS [23]; (2) rectal administration of lidocine in IBS patients decreased rectal sensitivity to intraluminal distention [24]; (3) glycerol instilled into the rectum induced visceral hypersensitivity [25]; and (4) low grade inflammation of intestinal mucosa has been verified by several studies of IBS [26]. Evidence for the hypothesis of the peripheral sensitization is seen in patients with postinfectious IBS (PI-IBS) who give a preceeding history of acute GI infection prior to the onset of their IBS symptoms [27]. Barbara et al. [28] have shown that increased mast cells have been observed

in the colonic mucosa in PI-IBS patients and that close proximity of mast cell and nerves in the colon was correlated with severity of abdominal pain. Gecse et al. [29] reported that mucosal application of fecal supernatants from IBS patients with diarrhea evoked colonic hypersensitivity in mice, which effect was associated with serine protease activity mediated through protease-activated receptor 2 (PAR-2). PAR-2 is expressed by nociceptive neurons and activated during inflammation by proteases from mast cells, the intestinal lumen, and the circulation.

Interestingly, peripheral administration of corticotrophin-releasing hormone (CRH), which activates the hypothalamic-pituitary-adrenal axis and is considered to be a major mediator of stress responses, induced rectal hypersensitivity after repetitive painful rectal distention in animal models [30] and humans [31]. On the other hand, peripheral administration of α -helical CRH, a non-selective CRH receptor antagonist, resulted in reduction of enhanced visceral pain perception as well as negative mood in response to gut stimulation in patients with IBS [32]. These findings indicate that both central and peripheral modulation may contribute to abnormal visceral perception in IBS. Thus, visceral hypersensitivity observed in IBS patients may be heterogeneous pathophysiological findings.

Relationships between Visceral Hypersensitivity and Clinical IBS Symptoms

No consensus has been established so far on relationships between visceral perception and symptom severity in patients with IBS although visceral hypersensitivity has been considered to be one of major pathophysiology for IBS. Drossman et al. [33] reported that IBS severity was weekly correlated with visceral hypersensitivity to rectal balloon distention. In a recent study [34], a multivariate analysis revealed that abdominal pain and bloating severity were independently associated with altered rectal perception observed in patients with IBS. In contrast, Lembo et al. [35] reported that IBS severity did not predict the development of rectal hypersensitivity to repetitive sigmoid distention. Moreover, no significant correlation was found between rectal threshold and either IBS symptom intensity in another study [36]. Likewise in children with IBS and functional abdominal pain (FAP), rectal hypersensitivity was not associated with severity of GI symptoms [37], suggesting that IBS symptom severity might be more influenced by other factors in childhood.

With respect to another site of the large intestine, the descending colon, our research group confirmed that pain threshold to intraluminal distention was significantly correlated with abdominal pain or overall symptom severity in patients with IBS despite subtypes of bowel habit [13]. Interestingly, we also found that abdominal pain severity was positively correlated with colonic motility in IBS patients with diarrhea (IBS-D) alone [13]. On the other hand, abdominal bloating severity was negatively correlated with colonic motility in IBS with constipation (IBS-C) alone [13].

These results suggest that not only visceral hypersensitivity but also other factors such as altered GI motility and psychological abnormality might be more or less associated with development of IBS symptoms.

Future directions

Novel therapeutic approaches for abnormal visceral sensitivity in IBS have been investigated in both basic and clinical settings (Table 1) [38]. Treatment with interpersonal psychotherapy [39] or serotonin selective reuptake inhibitor (SSRI) antidepressants [40] failed to change in rectal pain threshold to balloon distention despite clinical improvement in patients with IBS. However, it has been reported that kappa agonist fedotozine [41] or melatonin [42] relieved pain hypersensitivity to colonic distention in patients with IBS. Delvaux et al. [43] reported that 5-HT_3 antagonist alosetron also increased rectal pain threshold in IBS-D patients. During treatment with a tricyclic antidepressant, amitriptyline in patients with IBS-D, not only clinical symptoms improved but also rectal pain threshold significantly increased [44]. Furthermore, Lea et al. [45] found that gut-focusing hypnotherapy normalized visceral sensitivity with improvement of GI and psychological symptoms in patients with IBS. Overall, these findings indicated that visceral sensitivity observed in IBS can be manipulated by pharmacological or psychological intervention. Future clinical trials are awaited to determine whether changes in visceral sensitivity would be considered as one of reliable biological markers for improvement of IBS symptoms.

In conclusion, visceral hypersensitivity is one of most frequent findings and may play a major role in development of symptoms in patients with IBS. The implication of this idea is that it may be advantageous to target pain sensitivity for treatment of IBS. Further studies are needed to clarify the precise mechanism of visceral pain modulation in the brain-gut link.

Table 1. Novel candidate therapeutic agents for visceral hypersensitivity in IBS.

Opiates
κ1-opioids
μ-opioids
Serotonergic and adrenergic receptor modulators
5-HT_3 receptor antagonists
5-HT_4 receptor agonists
a_2-adrenergic receptor agonists
Antidepressants
Tricyclics
Selective serotonergic reuptake inhibitors
Serotonin and noradrenalin reuptake inhibitors
Neuropeptide receptor modulators
Neurokinin 3 receptor antagonists
CRH1 receptor antagonists
Others
Somatostatin analogue
Cholocystokinin (CCK)-1 antagonists
Melatonin

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Central Serotonin Neurotransmission Disorders Correlate with Visceral Perception and Psychological Characteristics in Patients with Functional Dyspepsia

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Background & Aims: Visceral perception of functional dyspepsia (FD) is based on the brain-gut interaction via various neurotransmission pathways. Peripheral or central serotonergic abnormalities are associated with the pathophysiology of functional gastrointestinal disorders or psychiatric depression and anxiety. To examine the roles of the cerebral serotonin (5-HT) neurotransmission systems in visceral perception of FD patients, we examined both 5-HT transporter (5-HTT) binding potential in the brain and the correlation between differences between patients and controls in 5-HTT binding potential and abdominal symptoms. **Methods:** Patients with FD diagnosed according to the Rome III criteria (N=9, female: 6, age range 25-61 yrs) were recruited for this study. There were 9 healthy controls (female: 3, age range 36-76 yrs). To measure 5-HTT binding potential with region-of-interest data in areas of the thalamus, putamen, caudate, amygdala, midbrain, and cerebellum (as a reference region), positron emission tomography (PET) with [^{11}C]N,N-dimethyl-2-(2-amino-4-cyanophenylthio) benzylamine ([^{11}C]DASB), which binds specifically to 5-HTT, was performed. We used the Multi-linear Reference Tissue Mode method within the standard software package of PMOD Technologies for analysis of [^{11}C]DASB with reference to the co-registered MRI images. Clinical symptoms were evaluated on the Gastrointestinal Symptoms Rating Scale (GSRS) including subscales for abdominal pain and indigestion. Depression and anxiety were evaluated on the Self-Rating Depression Scale and the State-Trait Anxiety Inventory. **Results:** All scores for abdominal pain, indigestion, depression, and anxiety were higher for FD patients than for controls ($p<0.01$). In FD patients, the binding potential of [^{11}C]DASB in the midbrain ($p=0.001$) and amygdala ($p=0.065$) was higher than in the corresponding areas in controls, while there were no differences between the groups in the thalamus, putamen, or caudate. Binding potential of [^{11}C]DASB in the midbrain was correlated with total GSRS ($p=0.018$, $r=0.572$), indigestion ($p=0.021$, $r=0.565$), and abdominal pain ($p=0.091$, $r=0.420$) scores, while in the amygdala it was correlated with total GSRS ($p=0.080$, $r=0.426$), indigestion ($p=0.057$, $r=0.469$), depression ($p=0.091$, $r=0.413$), and anxiety ($p=0.096$, $r=0.406$) scores. **Conclusion:** These findings suggest that in FD patients there are disorders of central 5-HT neurotransmission, especially in the midbrain and amygdala, which are correlated with their visceral symptoms and psychological characteristics.

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Evidence for Altered Central Noradrenergic Modulation in Irritable Bowel Syndrome (IBS)

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Background: The importance of central noradrenergic functions in IBS has been implicated, but has not been directly assessed. **Aims:** To study the effect of pharmacologic modulation of central noradrenergic activity on brain responses and associated subjective responses in IBS and compare to healthy control subjects (Ctrls). **Methods:** In a double-blind study, 11 IBS patients (6 men) and 11 Ctrls were studied 3 times, with an auditory vigilance task after ingestion of the α2 adreno receptor (α2AR) antagonist yohimbine (YOH; increases presynaptic NE release), the α2AR agonist clonidine (CLO; reduces NE release via presynaptic α2AR and blocks postsynaptic α2AR) or placebo. Plasma norepinephrine (NE), blood pressure, self-rated mood, and [18F] fluorodeoxyglucose (FDG) positron emission tomography (PET) images of cerebral glucose metabolism, which served as an index of relative regional brain activity, were acquired. **Results:** IBS patients had significantly higher plasma NE levels (all $p<0.05$) than Ctrls both before and after ingesting all three drugs. Both noradrenergic drugs produced expected effects on plasma NE, blood pressure, mood and brain activity. YOH increased anxiety and plasma NE more in IBS patients than Ctrls, and the increases were correlated with each other ($r=.63$). Connectivity analyses indicated a functional circuit in dorsal brainstem including locus coeruleus (LCC), amygdala and infragenual anterior cingulate cortex (iACC). YOH-mediated *reduction* of activity in this arousal network was stronger in all three regions of Ctrls (consistent with reduced presynaptic α2AR-mediated in IBS), whereas clonidine-mediated *increased* activity was stronger in the iACC and amygdala of IBS patients (consistent with greater noradrenergic tone). In Ctrls, but not IBS patients, activation of amygdala and iACC were inversely correlated with activation of the rostral ACC, and anxiety covaried directly with activity in limbic and right frontotemporal cortices, but indirectly with activity in left frontotemporal cortex. The latter finding is consistent with expected relationships between anxiety and the frontal laterality of brain activity in Ctrls, but not IBS patients. **Conclusions:** IBS patients had reduced responsiveness or downregulation of presynaptic inhibitory α2ARs as compared to Ctrls, resulting in increased plasma levels of NE and increased noradrenergic tone within central arousal circuits (amgydala, iACC, LCC). Activity in these circuits, which is correlated with anxiety, is biased toward greater adrenergic excitability and/or reduced descending inhibition from rostral cingulate and prefrontal cortices in IBS.

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Evidence for Altered Brain Circuits Underlying Selective Attention to Negative Emotional Stimuli in IBS

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BACKGROUND: Hypervigilance and attentional bias towards visceral sensation has been implicated in central pain amplification in IBS. AIM: To identify the neurobiological substrate mediating attention bias between IBS and healthy controls (Ctrls). METHODS: Brain activity in 23 female Rome+ IBS patients and 15 healthy women controls was studied using a Siemens Allegra 3T MRI scanner, using validated emotional reactivity (Emotional Matching vs. Forms Matching) and modulation (Emotional Labeling vs. Gender Labeling) paradigms that involve the viewing and labeling of negatively valenced emotional faces to activate brain circuits involved in emotion processing and arousal. Reaction Time (RT) was measured via Superlab presentation software. Paired group t-tests and a contrast analysis using a random effects general linear model were applied to test for difference in reaction time due to the interaction of group and condition. SPM5 was used to assess the relationship between reaction time and the brain activity and to test for group differences in these correlations using a false discovery rate of 5%. RESULTS: Both IBS and Ctrls showed significantly slowed responses during emotion matching and emotion labeling tasks compared to the respective control tasks (p's<.001). There was an observable trend for IBS patients to have slower RTs during all conditions, however, these differences only achieved statistical significance during emotion matching and labeling (p's<.01). Across all tasks, group differences were observed in the relationship between the RT and the medial prefrontal cortex (mPFC)/rostral anterior cingulate cortex (rACC), subgenual ACC, dorsal and lateral PFC, hippocampus, and dorsal pons. Examining the within group correlation with RTs revealed that IBS patients had more robust correlations whereas no regions could be considered significantly correlated in Ctrls. Further exploring these results by extracting the correlations (betas) from the representative mPFC voxel using the VOI toolbox in SPM revealed a moderately strong negative correlation between RT and mPFC/rACC for IBS ($r=-.38$, $p<.001$) but not for Ctrls ($r=-.07$, $p=.56$). CONCLUSIONS: IBS patients demonstrated selective attention biases primarily towards negative emotional stimuli in comparison to Ctrls. The group differences observed in the correlation between RT and PFC regions and the inverse correlation of RT and mPFC in IBS subjects, suggests that slower RTs in IBS are associated with reduced engagement of a PFC region involved in corticolimbic inhibition.

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Impact of Serotonin-3 Receptor Gene Polymorphism On Brain Activation By Rectal Distention in Human

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Background & Aims: Serotonin (5-HT)-related genes are the candidates that regulate the reactivity to stimulus in irritable bowel syndrome (IBS). The 5-HT3 receptor antagonists are used for the treatment of IBS. We previously reported that C allele of the 5-HT3B gene (HTR3B) polymorphism rs1176744 is more common in IBS population (Gastroenterology 132: A134-5, 2007). This variant dramatically augments the signaling of the 5-HT3 receptor (Proc Natl Acad Sci U S A 105: 722-7, 2008). We tested our hypothesis that C allele of HTR3B differentially activates regional brain to the rectal distention in human. Methods: Twenty-eight subjects without any organic disorders participated in this study. This study was approved by the Ethics Committee and all subjects gave the written informed consent. DNA was extracted from the peripheral blood. Using polymerase chain reaction, genotype of HTR3B was determined. Individuals with A/A genotype (n = 14) and individuals with C allele (genotype A/C and C/C, n = 14) were compared. Barostat bag was inserted to the rectum. The bag was intermittently inflated with no (0 mmHg) or intense (40 mmHg) stimulation with random order. Radioactive H2[15-O] saline was injected at the bag inflation and positron emission tomography was performed. Changes in rCBF were analyzed using statistical parametric mapping 2. Results: Intense rectal distention induced significant activation in the thalamus, insula, anterior cingulate cortex, and precuneus in both A/A subjects and A/C + C/C subjects ($p < 0.0001$). Subtraction analysis (image at 40 mmHg - image at 0 mmHg) differentiated activation pattern between the genotypes. A/C + C/C subjects showed significantly more activation in the right amygdala, left insula ($p < 0.0001$), and left orbitofrontal cortex (BA11, $p = 0.0001$) than A/A subjects. Conversely, AA subjects showed significantly more activation in the right dorsolateral prefrontal cortex (BA9) and right precuneus ($p < 0.0001$) than A/C + C/C subjects. Conclusion: These data suggest that individuals with 5-HT3 receptor gene polymorphism presumably with enhanced function respond to the gut-derived signal more in the brain regions of negative emotion, body recognition, and discrimination of the stimulus value. HTR3B polymorphism may partially predict the individual effects of 5-HT3 receptor antagonists in IBS.

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Neural Correlates of Sensory & Affective Pain Dimensions in Functional Dyspepsia: A $H_2{}^{15}O$-PET Study

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Background The lateral (somatosensory cortex, SI/SII) & medial pain system (anterior cingulate cortex) are the neural correlates of the sensory-discriminative & affective-motivational pain dimension, respectively. However, these findings are based almost exclusively on the somatic pain literature. ***Aim*** To study the neural correlates of sensory & affective pain dimensions in Functional Dyspepsia (FD). ***Methods*** Brain $H_2{}^{15}O$-PET was performed in 25 FD patients during 3 conditions: no distension (baseline), distension at discomfort threshold & sham. Sensory & affective pain dimensions were measured using Visual Analog Scales (VAS, range 0-150). Data were analyzed in SPM2 with threshold $p_{uncorr}<.001$. Sensory & affective VAS scores were correlated with mean brain activity during baseline, distension & sham and with contrasts distension>baseline & sham>baseline. ***Results*** ***Behavioural*** Mean sensory & affective VAS scores were 107±46 & 120±26, respectively. ***Imaging*** results are summarized in the table. Sensory pain scores correlate with activation in the lateral pain system, but also with regions reported to be involved in affective (hippocampus, cingulate subregions, orbitofrontal cortex), cognitive (cingulate, dorsolateral prefrontal) and modulatory (cingulate, dorsomedial prefrontal) aspects of pain in the somatic pain literature. Affective pain scores correlate with activation in only a few regions, some of which have been reported to be involved in affective pain dimensions (lateral orbitofrontal cortex, anterior cingulate cortex). ***Conclusion*** In FD, mainly sensory pain scores correlate with brain activation in several regions, including the lateral pain system but also affective and cognitive areas.

were: "made to have intercourse/oral/anal sex against will" (46.6%), "fondled under force/threat" (41.8%) and "having seen/handled dead bodies not in a funeral" (40.4%). The TQ also identified high prevalence of traumas (e.g., sex against will because of physical force/threat (49.4%), sexual harassment (65.1%) and domestic violence (48.2%)), with many reporting occurrence during military service (41.5%, 64.8% and 60.0% respectively). Almost 34% also reported history of childhood sexual abuse. Overall, IBS cases were significantly more likely to experience 9 of 18 THQ traumas, with another 4 closely approaching significance. Excess IBS risk conveyed by selected traumas was modestly increased in age- and ethnicity-adjusted model, with 11 traumas conveying significant risk (OR=1.72 - 2.43). Women veterans with IBS were also more likely than those without IBS to have PTSD (22.1% vs. 10.7%, p<0.006) and depression (44.2% vs. 30.0%, p=0.01). However, the excess IBS risk was only slightly attenuated after adjusting for these risk factors. Conclusion-A high prevalence of IBS, PTSD, and trauma was observed among women veterans. The most commonly reported traumas were sexual, with 49.4% of all women veterans reporting being forced to have sex during their military service. A history of many traumas was associated with an approximately 2-fold increased IBS risk. However, neither PTSD nor depression seems to explain this association.

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The Effects of *Bifidobacterium breve* On Gastrointestinal Symptoms, Cytokines, Fecal Microbiota and Organic Acids in Irritable Bowel Syndrome

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Background: Earlier studies support probiotics as the useful agent for treating patients with irritable bowel syndrome (IBS) but simultaneous changes in intraluminal environment, cytokines, and symptoms by probiotics are unknown. We tested our hypothesis that the above factors are simultaneously improved by Bifidobacterium breve. Methods: Subjects were 54 Rome II-defined IBS patients. IBS subtypes (constipation: C, diarrhea: D, and mixed: M) were classified with Rome III. Subjects were randomized to receive Bifidobacterium breve Yakult (n=27, 11 men, 16 women, C6/D10/M11) or placebo (n=27, 11 men, 16 women, C9/D8/M10) for 8 weeks. Primary endpoint was IBS symptoms assessed with Self-reported IBS Questionnaire (SIBSQ). Secondary endpoints were quality of life (QOL) and negative emotion. Stool sampling for analysis of intestinal microbiota and organic acids, blood sampling for measuring cytokines (tumor necrosis factor-alpha, transforming growth factor-beta), and abdominal X-ray film for analyzing bowel gas volume were performed before and at after the treatment. Results: Composite score for abdominal pain, discomfort, and loose stool of SIBSQ in B. breve group significantly improved compared with that in placebo group (ANOVA: period effect; p<0.0001, group x period interaction; p=0.036). ANOVA of TNF-alpha also showed significant group x period interaction (p=0.015). The 15 bacterial counts and levels of 8 organic acids (acetic, succinic, valeric, iso-valeric, formic, butyric, propionic, and lactic acids) were not changed by administration of B. breve. However, significant correlation between changes (before and after the treatment) in SIBSQ score and changes in acetic acid was detected in placebo (r=0.382, p=0.05) but not in B. breve. Conclusion: These data suggest that administration of B. breve to IBS alleviates GI symptoms simultaneously with improved level of TNF-alpha. Fecal acetic acid as the product of microbiota is likely to influence on IBS symptoms in the natural course but not in the administered state with probiotics.

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Implementation of National Dyspepsia Guidelines to Reduce Prescribing and Return Patients to Self Care: Results from An Educational Intervention and Prospective Clinical Audit in England

Mark Connolly, Aomesh Bhatt

Background: Clinical guidelines from the UK National Institute for Health and Clinical Excellence (NICE) for the Management of dyspepsia in adults in primary care suggest the need for an annual review of patients requiring long-term management of dyspepsia with the aim of stepping down (S-D) or stepping off (S-O) treatment, and returning patients to self care for breakthrough events. Aim: To evaluate the long-term effectiveness of an educational strategy aligned with NICE clinical guidance of S-D or S-O treatment and encouraging patients to return to self care. The results described here are the long-term follow-up from an earlier educational intervention study. Method: We report findings from 2.5 years follow-up based on a subset of patients who had successfully been S-D or S-D long term proton-pump inhibitors (PPI) treatment by a nurse led educational strategy which followed NICE guidelines (2004). The original audit published elsewhere, (Evans N.,BJHCM 2007;13:425-430), was a prospective multi-centre audit that recruited patients with non-ulcer dyspepsia (NUD) and Gastro-oesophageal reflux disease (GORD) treated with PPI for >2 months from nine primary care practices in a suburb of London. Patients were offered a treatment change to low-dose PPI (step down) plus alginate or alginate (Gaviscon Advance) alone (step off). Exclusion criteria were *H. pylori* infection, duodenal or gastric ulcer and complicated dyspepsia. Results: The mean age of participants at baseline was 64 (SD 13.5), 49% male and 93% receiving PPI for >6 months with no difference between S-D and S-O groups. Of the eligible patients 40% (n=112) and 28% (n=77) agreed to S-D and S-O therapy, respectively, of which 93% (n=104) were successfully stepped down to low-dose PPI plus alginate and 78% (n=60) stepped off onto alginate alone. At 2.5 years following the educational intervention 81% (n=153) of patients who had successfully completed the initial step down/step off programme had retained their status. With respect to S-D and S-O therapy recommendations 88% (n=92) and 66% (n=40) of subjects maintained the alternative therapy option at 2.5 years, respectively. Conclusions: The results indicate that in appropriate patients, educational interventions are effective for reducing long term PPI prescribing. A higher proportion of subjects stepping down maintained the recommended therapy. The results highlight that reducing unnecessary long term use of PPIs and enabling patients to return to self care with alginates is unlikely to compromise symptom control in patients with reflux disease and is also likely to offer valuable cost-savings.

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Impact of Baseline Severity On the Performance of IBS Clinical Trial Endpoints: Results of the ROME Foundation Endpoints Working Group Meta-Analysis

Brennan M. Spiegel, Roger E. Bolus, Michael Camilleri

Background: It remains unclear how best to measure patient reported outcomes (PROs) in IBS. The performance of binary PROs (*e.g.* "adequate relief") as trial endpoints may be influenced by baseline symptom severity. An alternative is to measure improvement on a linear severity scale, and to define "response" over time of treatment as ≥50% improvement. **Aim:** To perform a meta-analysis of clinical trials to measure the impact of baseline pain severity on binary endpoints vs. the 50% improvement criterion. **Methods:** We pooled patient-level data from 4 pharmaceutical companies comprising 12 previously conducted IBS trials involving 10,066 participants. In addition to demographics and symptom profiles, each study included a baseline and end-of-study measure of abdominal pain, and an end-of-study binary global endpoint. We adopted pain intensity as a surrogate for severity, and created a harmonized modified T-scale for "pain severity" (mean=100; SD=10) spanning all trials. We trichotomized patients into baseline severity tertiles (mild, moderate, severe), and compared response rates across tertiles for the 2 endpoints (binary vs. ≥50% improvement) using chi-squared. We performed multivariate logistic regression to measure the effect of baseline severity on responses while adjusting for IBS sub-type, treatment status, age, sex, and IBS duration. We used an *a priori* criterion to define minimal clinically important difference, defined as a difference ≥5 points on the pain severity T-scale (*i.e.* effect size ≥0.5) in responders vs. non-responders. **Results:** There were 9044 evaluable subjects (mean age= 44; 85% F; 58% IBS-C; 31% IBS-D). Using the binary endpoint, the proportion responding in the mild, moderate, and severe groups was 42.2%, 40%, and 38.2%, respectively (p= 0.0008). In logistic regression, there was no effect of baseline severity on binary response (OR=0.995; CI=0.99-1.0; p=0.07). The proportions reaching 50% improvement in pain were 45.4%, 40.9%, 41.3%; in logistic regression, there was a small yet significant impact of baseline severity (OR=1.04; CI=1.03-1.05; p<0.0001). The absolute difference in T-scale scores between responders and non-responders was 0.6 and 0.7 points for binary and 50% improvement, respectively. Neither difference met criteria for clinical relevance. **Conclusions:** The relationships between baseline severity and either the global binary or 50% improvement endpoints are statistically significant, but not clinically relevant. This large meta-analysis provides further evidence that both endpoints are valid as primary endpoints for IBS clinical trials. [Work by Rome Foundation Endpoints Committee]

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Performance of Competing IBS Trial Endpoints Depends On IBS Subtype: Results of the ROME Foundation Endpoints Working Group Meta-Analysis

Brennan M. Spiegel, Roger E. Bolus, Michael Camilleri

Background: It is unclear how best to measure patient reported outcomes (PROs) in IBS trials, and whether IBS subtype should influence the choice of PRO. Binary PROs (*e.g.* adequate relief) may fail to detect minimal clinically important differences (MCID) in symptom improvement. An alternative is to measure improvement on a linear severity scale, and to define response over time of treatment as ≥50% improvement. **Aim:** To perform a meta-analysis of clinical trials to measure the ability of binary endpoints vs 50% improvement criterion to detect MCIDs in symptoms stratified by IBS subtype. **Methods:** We pooled patient-level data from 4 companies comprising 12 IBS trials (N=10,066). Each study included baseline & end-of-study symptom profiles, and an end-of-study binary global endpoint. We created harmonized T-scales for each symptom (mean=100; SD=10) across trials. For the 50% improvement criterion, we adopted abdominal pain intensity as a surrogate for symptom severity, and defined responders as those improving ≥50% over baseline on the pain T-scale. We compared the proportion achieving an MCID for each symptom stratified by responder status for each endpoint (binary vs. 50% improvement), with MCID defined as a net ≥5 point improvement in scale score (i.e. effect size=0.5). **Results:** There were 9044 evaluable subjects (mean age=44; 85% F; 58% IBS-C; 31% IBS-D). The Table displays the results. In IBS-D & IBS-C, both endpoints identified statistically significant differences in the proportion achieving an MCID for pain, bloating, and stool frequency. However, consistency, urgency, and incomplete evacuation were identified in IBS-D, not in IBS-C. The proportion achieving MCID was considerably higher in IBS-D vs IBS-C with both endpoints. **Conclusions:** Global binary & 50% improvement endpoints performed similarly in discriminating between those achieving MCID symptom response vs non-responders, especially for pain, bloat, and urgency. However, there was better discriminant spread in IBS-D vs IBS-C. This suggests that more sensitive endpoints might be necessary for IBS-C. [Work by Rome Endpoint Committee]

Spread in Proportion of Patients with MCID for Bowel Symptoms by IBS Subtype and Response Definition (*=p<0.05).

	IBS-C		IBS-D	
	Binary	50%	Binary	50%
Pain	38%*	56%*	36%*	60%*
Bloat	38%*	52%*	39%*	50%*
Stool Freq	5%*	3%*	28%*	32%*
Stool Consist	10%*	8%	32%*	30%*
Urgency	1%	9%	34%*	41%*
Incomp Evac	6%	13%*	20%*	26%*
Strain	10%	16%*	1%	4%