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Focal corticarl dysplasia in epilepsy is associated with GABA increase

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ABSTRACT

Purpose: Focal cortical dysplasia (FCD) is a major cause of drug-resistant epilepsy; however the underlying epileptogenic mechanisms of FCD metabolism in epilepsy patients remain unclear. The aim of this study is to detect alterations of γ-aminobutyric acid (GABA), glutathione (GSH), and the composite of glutamate and glutamine (Glx) in MRI-typical and neuropathologically confirmed FCD-associated epilepsy using Hadamard Encoding and Reconstruction of Mega-Edited Spectroscopy (HERMES).

Materials and methods: Fourteen epileptic patients suspected to be caused by FCD and 14 healthy controls were enrolled prospectively in this study; all subjects underwent a 3 T MRI scan, including 3D T1 weighted imaging and HERMES. The GABA signal detected by HERMES also contains signals from macromolecules and homocarnosine, so it is referred as GABA+. Signals of GABA+, GSH and Glx detected by HERMES from tumor foci, contralateral cerebral regions, and healthy controls were quantified using Gannet. Fitting errors and signal to noise ratios (SNRs) of GABA + signals were also recorded. Differences of GABA+, GSH, Glx, fitting error and SNR of GABA + among three groups were analyzed using linear mixed effects models.

Results: Twelve FCD-associated epilepsy patients (7 females, aged 21.9 ± 9.3 years) and 12 matched healthy controls (7 females, aged 22.8 ± 9.8 years) were finally enrolled in this study. ANOVA results indicated that GABA levels were significantly increased in FCD foci compared with contralateral regions ($p = 0.008$) and with healthy controls ($p = 0.003$), while no difference was found in GSH and Glx levels. No difference of fitting errors or SNR of GABA + was found among FCD foci, contralateral regions and healthy controls.

Conclusions: Increased GABA levels were found in FCD foci that indicated GABA may play a central role in the pathophysiology of FCD patients with epilepsy.

1. Introduction

Focal cortical dysplasia (FCD) is malformation of the neocortex caused by abnormal neuronal migration, which is a major cause of drug-resistant epilepsy in childhood and early adulthood (Blumcke et al., 2011). However, the underlying mechanism of how metabolism disturbances in FCD-associated epilepsy patients remains unclear. Previous studies have indicated metabolic dysfunction in cortical organization could render neurons epileptogenic (Lin Lin Lee et al., 2018; Patel, 2018; van Karnebeek et al., 2018). Gamma-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in central nervous system, maintains the inhibitory tone that counterbalances neuronal excitation (Treiman, 2001). Glutamate is the main excitatory neurotransmitter in the cerebral cortex, making up a balance between excitation and inhibition combined with GABA. When this balance is perturbed, seizures may ensue (Treiman, 2001). Glutathione (GSH) is an antioxidant, which is capable of reducing damages to specific neuron caused by reactive oxygen species (ROS). GSH depletion can enhance oxidative stress, and excessive ROS may trigger the degenerative process of epilepsy (Huusko et al., 2015). More and more evidences demonstrated that GABA (Treiman, 2001), glutamate (Meldrum, 1994) and GSH (Cárdenas-Rodríguez et al., 2014; Mueller et al., 2001) can play vital roles in the

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mechanism of epilepsy. However, alterations of these metabolites in epilepsy still remain controversy, and the metabolite variations in FCD-associated epilepsy were rarely reported.

The concentration of GABA and GSH and in the brain is too low to be reliably detected using conventional single-voxel magnetic resonance spectroscopy (MRS). The edited MRS, e.g. Mescher-Garwood Point-resolved Spectroscopy (MEGA-PRESS), was thus developed for specific detection of low-concentration metabolites, including GABA (Gong et al., 2018; Mescher et al., 1998), Glx and GSH (Dhamala et al., 2019; Sanaei Nezhad et al., 2017) etc. Hadamard Encoding and Reconstruction of Mega-Edited Spectroscopy (HERMES) applies multiple orthogonal editing encoding, allowing GSH, GABA and Glx (composite of glutamate and glutamine) spectra to be simultaneously reconstructed from one single sequence (Chan et al., 2019; Gong et al., 2020; Saleh et al., 2016). The aim of this study is to detect alterations of GABA, GSH and Glx in MRI-typical and neuropathologically confirmed FCD-associated epilepsy using HERMES.

2. Materials and methods

2.1. Human subjects

This study was ethically approved by the research ethics committee of Shandong Provincial Hospital and written informed consent was obtained from all participants. The epilepsy patients enrolled in this study met these criteria: diagnosis of FCD on conventional MRI with the following signs, 1) cortical thickening, 2) intracortical signal, or 3) gray-white blurring. The epileptogenic foci were further confirmed by electroencephalography (EEG) with spike and wave activity; age over 14 years old; candidate for resection in two weeks. 14 patients (7 female, aged 14–43 years) who were scheduled to receive surgery for suspected diagnosis of FCD-associated epilepsy and 14 age- and sex-matched healthy controls were enrolled prospectively in this study. Some of the patients were treated with multiple anti-epileptic drugs for varying durations, the most anti-epileptic drugs used by patients in this study mainly included: 1) valproic acid, 1000 ~ 2000 mg/day; 2) levetiracetam, 1500 ~ 1750 mg/day; 3) oxcarbazepine, 600 ~ 1200 mg/day.

2.2. Magnetic resonance imaging and spectroscopy

All MR data were acquired using a 32-channel phased-array head coil on a 3 T MR scanner (Skyra, Siemens, Erlangen, Germany), including 3D T1 weighted imaging and HERMES. The parameters of 3D T1 weighted imaging included: the T1-weighted magnetization-prepared rapid gradient-echo sequence was used; repetition time/echo time (TR/TE) = 2300/2.29 msec; slice thickness = 1.0 mm; field of view = 24 × 24 cm^2; matrix size = 256 × 256; flip angle = 8°; and acquisition time was ~ 5 min. The parameters of HERMES were as follows (Gong et al., 2020): TR/TE = 2000/80 ms; number of average = 320; data point = 2048; spectral width = 2 kHz; voxel size = 3.0 × 3.0 × 3.0 cm^3; Siemens modified WET water suppression and automated shimming (~12 Hz water linewidth) methods were used; and acquisition time was ~ 10 min. All patients stopped taking medication at least 12 h before the MRS data collection. The regions of interest (ROIs) for HERMES were set at FCD foci, contralateral cerebral regions (CR) in patients as shown in Fig. 1a-c; for healthy control (HC), the ROIs were set one-to-one correspondence with the position of FCD foci, as illustrated in Fig. 1d.

The detected GABA, GSH and Glx signals in FCD, CR and HC were quantified using the Matlab-based (MathWorks, Natick, MA) analysis toolkit Gannet 3.1 (http://www.gabamrs.com/) (Edden et al., 2014). The GABA signal detected by HERMES might also contain co-edited signal from macromolecules and homocarnosine, so it is referred as GABA+ below. GABA+, GSH and Glx were quantified relative to water, as a concentration in institutional units (i.u.). The ratios of the integrals of GABA+ and water signals, making corrections for T1 and T2 relaxations and tissue composition, were used to calculate water-scaled

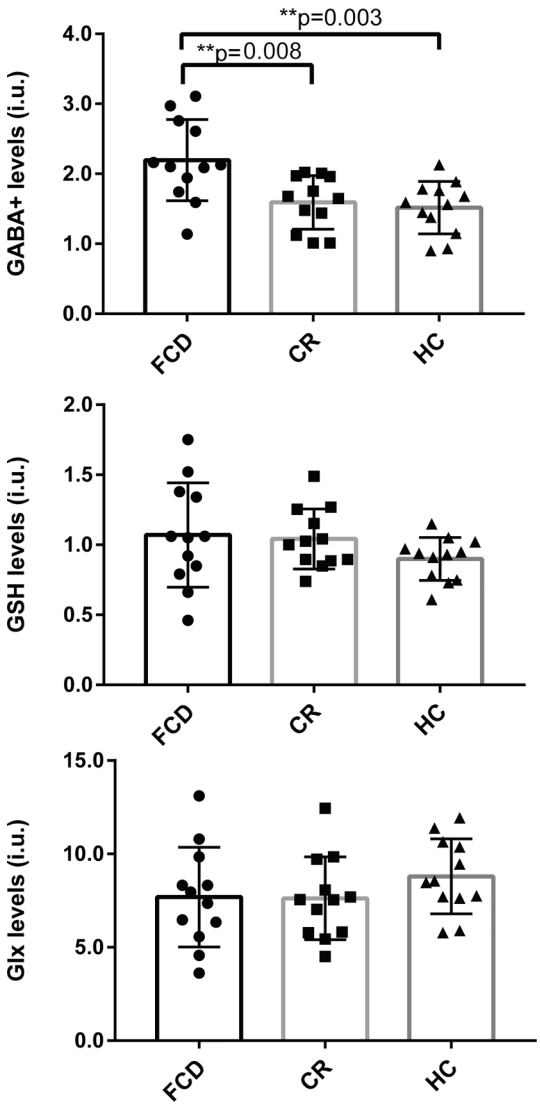

Fig. 1. T2-FLAIR image (a) of an FCD (with cortical thickening at the white arrow) -associated epilepsy patient, the regions of interest of HERMES in the patient (b and c) and in a matched healthy control (d). The mean (±standard deviation) GABA+ (e), Glx (e) and GSH (f) -edited spectra acquired by the HERMES sequence in FCD foci, contralateral regions and healthy controls.

GABA+ levels in institutional units (i.u.) as [GABA+] (Gasparovic et al., 2006; Mullins et al., 2014). Only spectra with a relative fitting error (FitError) of GABA + generated by Gannet smaller than 15% were enrolled in the final statistical analysis. The fitting errors and signal-to-noise ratios (SNR) of GABA + signals were also recorded.

2.3. Statistical analysis

Quantitative results are presented as mean ± standard deviation (SD). The differences of GABA+, GSH, Glx levels, GABA + fitting errors and SNR among the three groups were analyzed using linear mixed effects models: group was entered as a fixed factor, subject number was modelled as a random factor, if significant, the pairwise comparisons would be analyzed by the least significant difference (LSD) test. When compared between FCD foci and contralateral regions, epilepsy duration and frequency were modelled as covariates. Segmentation of T1-weighted images was performed using SPM 12. Statistical analyses were carried out by SPSS 22.0, and the threshold of significance was set at $P < 0.05$.

3. Results

The histopathologic results indicated that one case was low-grade glioma, not a FCD foci; another MRS data was removed because of the fitting error of GABA was bigger than 15%. So, 12 FCD associated epilepsy patients (7 females, aged 21.9 ± 9.3 years) were finally enrolled in this study, as listed in Table 1. Another 12 one-to-one matched healthy controls (7 females, aged 22.8 ± 9.8 years) were enrolled as controls.

Results of linear mixed-effects models indicated that there is a significant difference in GABA levels among FCD foci, contralateral regions and healthy controls ($F = 8.03$, $p = 0.003$), while no difference was found in GSH and Glx levels, as indicated in Table 2 and Fig. 2. The LSD results further revealed that GABA levels were significantly increased in FCD foci compared with contralateral regions ($p = 0.008$) and with healthy controls ($p = 0.003$). No difference of the GABA + fitting error or spectral SNR was found among FCD foci, contralateral regions and healthy controls (both $p > 0.05$ in Table 2).

Table 2
Mean and standard deviation of GABA+, GSH and Glx levels for FCD foci, CR and HC groups.

	FCD	CR	HC	F	p
GABA+ (i.u.)	2.19 ± 0.58	1.59 ± 0.38	1.51 ± 0.37	8.03	0.003
GSH (i.u.)	1.07 ± 0.37	1.04 ± 0.21	0.89 ± 0.15	1.43	0.261
Glx (i.u.)	7.68 ± 2.67	7.62 ± 2.22	8.79 ± 2.04	0.98	0.387
Fitting Error(GABA +)	9.55 ± 3.24	8.76 ± 2.54	8.78 ± 2.34	0.18	0.92
SNR(GABA +)	11.84 ± 2.84	10.53 ± 2.41	9.87 ± 2.56	0.55	0.65

4. Discussions

Our study showed that HERMES can be applied for simultaneous detection of GABA+, GSH and Glx signals in FCD-associated epilepsy patients. The results of statistical analysis indicated that GABA+ levels were significantly increased in epilepsy focal region of patients compared with contralateral regions and with healthy controls, while no significant alteration was found in GSH and Glx levels, suggesting that GABA may play a central role in the pathophysiology of FCD-associated epilepsy. As far as we know, this is the first time to detect the GABA, GSH and Glx alterations in FCD-associated epilepsy using edited MRS method of HERMES.

GABA, the main inhibitory neurotransmitter in the cerebral cortex, could counteract hyperexcitation in epilepsy. More and more evidences have indicated that GABA was centrally involved in the epilepsy process, and abnormalities of GABAergic function were found in FCD-associated epilepsy (Banerjee et al., 2020; Calcagnotto et al., 2005b; Crino et al., 2001; Medici et al., 2016; Treiman, 2001). However, the variations of GABA concentration in epilepsy are still controversy. Theoretically, dysfunction of GABA-mediated synaptic inhibition is believed to lead to hyperexcitability and ultimately seizure (Bhagat et al., 2020; Calcagnotto et al., 2005a), accompanied with the reduction of GABA inhibition (Treiman, 2001). Interestingly, in this study, higher GABA levels were found in FCD foci of epilepsy patients than that in contralateral regions or healthy controls. A previous research indicated that GABA levels were increased in epilepsy (Chowdhury et al., 2015a) or FCD-associated epilepsy patients compared to controls (Chowdhury et al., 2015b), and another literature illustrated that GABA inhibition enhanced in typical absence epilepsy (Cope et al., 2009). Similar results were also observed in studies on mice (Hamelin et al., 2021; Klaassen et al., 2006). Increased GABA synaptic activity could serve to dampen excessive excitability of cortical neurons in the FCD foci, but it could also promote neuronal network synchrony (Cepeda et al., 2020), which is related with the high frequency oscillations in epilepsy. Meanwhile, there was also research indicating no alterations of GABA levels in epilepsy (Simister et al., 2003), or different cerebral regions showed the opposite results (Hattingen et al., 2014).

The increased GABA + level in regions of FCD foci observed in this study could be due to multiple factors, including the increased synaptic/vesicular GABA, the increased GABA metabolism or reduced catabolism within cells, or a shift of GABA into a more visible pool (Stagg, 2014). It is difficult to distinguish with certainty among these possibilities at present. Seizure derived from FCD is mainly contributed by a receptor activation due to increased GABA levels, and the receptor was located at presynaptic inhibitory terminals (D'Antuono et al., 2004). Therefore, we speculated that synaptic/vesicular GABA would increase accordingly, which might support the conclusion that the increased GABA level enhanced inhibition in epilepsy associated with FCD.

Glutamate, a primary excitatory amino acid, was confirmed to be involved in epilepsy (Woo et al., xxxx) and plays a major role in the initiation and spread of seizure activity (Chapman, 2000). Glutamine, metabolized to glutamate by phosphate-dependent glutaminase, making up a glutamate-glutamine cycle, which is a key mechanism for control of glutamatergic neurotransmission. Changes of the cycle were frequently encountered in patients with epilepsy (Eid et al., 2016). Glutamate and glutamine were difficult to be separated in conventional or edited MRS because of overlapping peaks, and therefore typically reported as a combined signal of Glx. Previous MRS studies in idiopathic generalized epilepsies have reported increased Glx in frontal and thalamic regions (Helms et al., 2006; Simister et al., 2003), while no differences was found in FCD patients (Tschampa et al., 2015). Few studies were reported to focus on the Glx alterations in FCD-associated epilepsy. In this study, no difference of Glx was found among epileptogenic focus,

Table 1
Demographics and clinical information of FCD associated epilepsy patients.

No.	gender	Age (years)	duration	Frequency	IID	Seizure type	ID	EZ
1	**M**	15	10y	daily	LH, anterior	FIAS, FMS, FBTCS	LH, anterior	LH, Frontal
2	**F**	35	20y	daily	BH, temporal lobe	FIAS, FNMS, FBTCS	–	LH, Precuneus
3	**F**	19	2.5y	daily	LH	FIAS, FNMS, FBTCS	Bi	LH, Occipitotemporal
4	**F**	14	0.5y	weekly	LH, posterior	FIAS, FMS, FBTCS	LH	LH, Cuneus/Precuneus
5	**M**	20	1w	once	RH, frontal-temporal	FBTCS	–	RH, Temporal
6	**F**	16	4 *m*	4 times	RH, frontal-temporal	FBTCS	–	RH, Frontal
7	**M**	16	6 *m*	daily	RH, frontal-temporal	FIAS, FMS, FBTCS	RH	RH, Temporal
8	**F**	43	37y	daily	LH, central-parietal	FAS, FMS, FBTCS	LH	LH, Frontal
9	**M**	29	26y	daily	RH, frontal, midline	FAS, FMS, FBTCS	RH	RH, Paracentral lobule
10	**M**	17	1w	daily	Bi	FIAS, FMS	RH, posterior	LH, Cuneus/Precuneus
11	**F**	25	3y	daily	LH	FIAS, FMS, FBTCS	Bi	LH, Precuneus
12	**F**	14	4 *m*	weekly	LH, frontal-temporal	FIAS, FMS	–	LH, obital-opercular

Abbreviations: IID, interictal discharge; FAS, focal aware seizure; ID, ictal discharge; EZ, epileptogenic zone; LH, left hemisphere; FIAS, focal impaired awareness seizure; RH, right hemisphere; FMS, focal motor seizure; Bi, bilateral hemispheres; FNMS, focal nonmotor seizure; FES, focal epileptic spasm; FBTCS, focal to bilateral tonic-clonic seizure

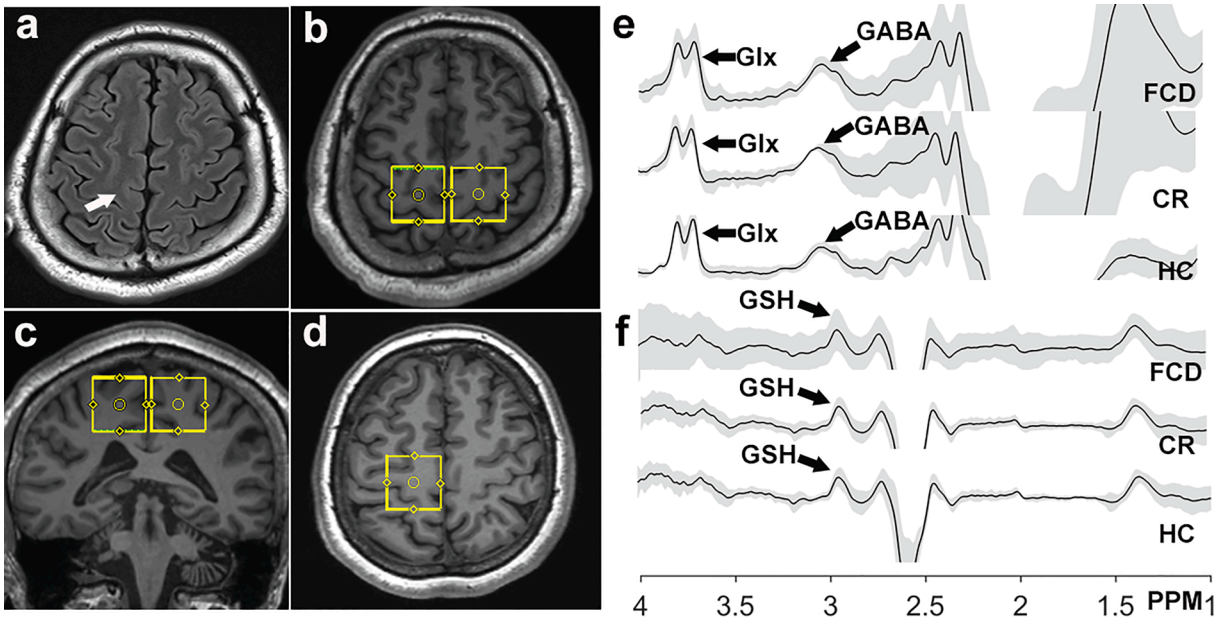

Fig. 2. Comparations of GABA+, GSH and Glx levels among the FCD foci, contralateral regions and healthy controls using ANOVA and the following LSD test. Results indicated that GABA + levels were significantly increased in FCD foci compared with contralateral regions ($p = 0.008$) and with healthy controls ($p = 0.003$).

contralateral regions, and healthy controls. Slow rates of glutamate-glutamine cycling were found in epilepsy patients, inducing decreased glutamine and increased glutamate contents (Petroff et al., 2002), which could account for this results to some extent. However, the opposite view also exists, a previous research indicated that glutamine in epilepsy was higher than controls (Chowdhury et al., 2015b).

Oxidative stress is regarded as a possible mechanism in the pathogenesis of epilepsy (Chang and Yu, 2010). GSH is an antioxidant, which is able to prevent damage of specific neuron caused by reactive oxygen species (ROS). GSH depletion can enhance oxidative stress, and excessive ROS may trigger the degenerative process of epilepsy (Huusko et al., 2015). One previous literature (Mueller et al., 2001) indicated that GSH levels were significantly reduced in the parietooccipital region in epilepsy patients, while no difference was shown between epileptogenic focus and the hemisphere without epileptogenic focus. However, the GSH in this study tended to be higher in FCD-associated epilepsy compared with healthy controls, even the difference was not statistically significant, which was in line with an erythrocyte GSH research (Menon et al., 2014). This discrepancy may be attributed to the differences of patient selection criteria and ROI positions, and GSH levels increased in epilepsy patients after receiving anti-epileptic drugs (Işık et al., 2015).

There are several limitations of this study. First, the sample size was small, only 14 MRI diagnoses of FCD epilepsy patients were enrolled in this study; but the tendency of increased GABA in epileptogenic foci of FCD derived from the results with good credibility, even further large-scaled prospective trials are still warranted to verify this. Second, the separated glutamate or glutamine signals cannot be obtained by HERMES, therefore, we are not able to verify the glutamate/GABA imbalance hypotheses in FCD-associated epilepsy in this study. Third, the fairly large voxel size ($3.0 \times 3.0 \times 3.0$ cm^3) of HERMES used in this study can usually be larger than the localized FCD foci, so the metabolite levels measured would suffered from partial volume effects from surrounding tissues. The previous study has demonstrated that the histopathologically normal tissue neighboring FCD regions may also harbor maldeveloped or underdeveloped GABAergic neurons (Han et al., 2019), and FCD studies (Hodozuka et al., 2006) on rats and clinical cases also confirmed that the presence of epileptogenecity not only in the lesion but also in the perilesional area. Therefore, the significantly increased GABA+ level observed in this study from the whole voxel around FCD foci may be contributed from both GABA+ level changes of FCD foci and surrounding tissues. Fourth, some antiepileptic drugs (e.g. gabapentin) will inhibit GABA uptake, resulting in an elevated concentration of GABA (Cai et al., 2012; Eckstein-Ludwig et al., 1999). All patients were stopped taking medicine 12 h before MR scan to minimize the influence on GABA levels, even no evidence was found that the medicine used in this study could affect the GABA levels. Besides, no significant difference in GABA level was found between healthy controls and contralateral regions in epilepsy patients treated with valproic acid, levetirecetam, or oxcarbazepine. Therefore, we believed the finding of increased GABA + levels in the FCD foci was convincible.

5. Conclusions

HERMES was able to detect alterations of GABA, GSH and Glx in FCD-associated epilepsy patients. Increased GABA level was observed, while no significant alteration of GSH and Glx levels was found in epilepsy patients in this study. The results indicated that GABA may play a central role in the pathophysiology of epilepsy.

Bhagat et al. (2021), Cárdenas-Rodríguez et al. (2014), Işık et al. (2015).

CRediT authorship contribution statement

Tao Gong: Conceptualization, Writing - original draft, Funding acquisition, Conceptualization, Writing - original draft, Funding acquisition. **Yubo Liu:** Resources, Visualization, Resources, Visualization. **Yufan Chen:** Resources, Data curation, Resources, Data Curation. **Liangjie Lin:** . **Youting Lin:** Data curation, Methodology, Supervision, Data curation, Methodology, Supervision. **Guangbin Wang:** Supervision, Project administration, Supervision, Project administration.

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Disclosure

None of the authors have any conflicts of interest to declare.

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