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Brain glucose metabolism is associated with hormone level in Cushing's disease: A voxel-based study using FDG-PET

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ABSTRACT

Chronic exposure to elevated levels of glucocorticoids can exert a neurotoxic effect in patients, possibly manifesting as molecular imaging alterations in patients. The aim of this study was to investigate the potential association between brain metabolism and elevated hormone level using ^{18}F-fluorodeoxyglucose positron emission tomography. We retrospectively enrolled 92 consecutive patients with confirmed diagnosis of Cushing's disease. A voxel-based analysis was performed to investigate the association between cerebral ^{18}F-fluorodeoxyglucose uptake and serum cortisol level. Relatively impaired metabolism of specific brain regions correlated with serum cortisol level was found. Specifically, notable correlations were found in the hippocampus, amygdala, and cerebellum, regions considered to be involved in the regulation and central action of glucocorticoids. Moreover, some hormone-associated regions were found in the frontal and occipital cortex, possibly mediating the cognitive changes seen in Cushing's disease. Our findings link patterns of perturbed brain metabolism relates to individual hormone level, thus presenting a substrate for cognitive disturbances seen in Cushing's disease patients, as well as in other conditions with abnormal cortisol levels.

1. Introduction

For nearly half a century, the brain has been recognized as a target organ for plasma glucocorticoids (Martignoni et al., 1992). Although the mechanism of central action of hormones derived from circulation is far from clear, an increasing number of studies have linked excessive plasma glucocorticoids with cognitive symptoms in otherwise normal subjects, as well as in patients with disorders in which glucocorticoids have been implicated, notably major depression, Alzheimer's disease, and organic psychoses (Belanoff et al., 2001). In particular, Cushing's disease (CD) presents a unique human model to investigate brain changes resulting from chronic endogenous cortisol overexposure (Newell-Price et al., 2006).

It is well-established that excessive glucocorticoids can exert a neurotoxic effect (McEwen, 2007). The cognitive impairments of CD patients include concentration, learning, and memory deficits, as well as mood disorders such as depression, euphoria, and anxiety (Forget et al., 2000). Besides these neuropsychiatric symptoms, excessive glucocorticoid exposure in CD patients can cause structural abnormalities in radiological brain images. Indeed, previous studies have demonstrated that brain volume (Bourdeau et al., 2002; Momose et al., 1971) is significantly decreased among patients with excessive glucocorticoid exposure. The hippocampus, a brain area involved in regulating the secretion of glucocorticoids (Herman et al., 2005; Jacobson and Sapolsky, 1991), has shown structural and functional changes in such patients (Maheu et al., 2008; Starkman et al., 1992). In general, the detection of perturbed brain structure and function by medical imaging is an important tool to explore mechanisms underlying the cognitive complaints of CD patients, and can also help to reveal how excessive hormone levels might interfere with brain health.

[^{18}*F*]Fluorodeoxyglucose positron emission tomography (FDG PET) presents an important method for metabolic brain imaging, and has been widely used in evaluating compromised brain function in Alzheimer's disease as well as other conditions manifesting in cognitive disorders (Habeck et al., 2012; Robert et al., 2012). To date, no studies have investigated the relationship between FDG PET measurements of brain metabolism and individual hormone level in CD patients using voxel-based methods. In the current study we enrolled a large

Abbreviations: CD, Cushing's disease; FDG PET, ^{18}F-fluorodeoxyglucose positron emission tomography; ACTH, adrenocorticotropic hormone; HPA, hypothalamic–pituitary–adrenal.

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consecutive cohort of CD patients for FDG PET investigation. We performed a voxel-based statistical comparison to identify the anatomical correlations between brain metabolism and individual hormone alteration in CD patients.

2. Materials and methods

2.1. Patients

The current study retrospectively enrolled 92 consecutive CD patients treated at Peking Union Medical College Hospital between January 2010 and January 2015. The patients included in this study met the following criteria: adults with confirmed diagnosis of CD; informed consent for a presurgical PET scan; presurgical examination for serum cortisol and serum adrenocorticotropic hormone (ACTH) levels; no prior craniotomy or stereotactic biopsy. All patients were diagnosed with CD at the Endocrinology and/or Neurosurgery division of our hospital (78 patients had a pathology-based diagnosis of a pituitary tumor). Laboratory tests of the 8 AM serum cortisol and ACTH concentrations were performed for all patients; the laboratory tests were obtained using standard procedures within 1 month of the PET acquisition. All research activities in this study were approved by the Ethics Committee of our hospital, and all patients provided informed consent.

2.2. Image acquisition

The PET data were acquired on a Biograph 64 TruePoint TrueV PET/CT system (Siemens Medical Solutions, Erlangen, Germany). FDG was produced on-site using a RDS-111 Cyclotron (CTI, Knoxville, TN, USA) and standard procedures for FDG production. Before the PET examinations, the patients were required to fast for at least 4 h; the level of blood glucose in each patient was confirmed to be within normal limits (<6.4 mM). We administered FDG intravenously at a dose of 5.55 MBq (0.15 mCi) per kilogram of body weight.

2.3. Spatial normalization and reference scaling of FDG PET images

Images from all subjects were registered at the Montreal Neurological Institute space using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) and spatially smoothed with a Gaussian kernel at a full width at half maximum of 6 mm. Considering the well-known variation of the baseline cerebral metabolism between subjects, FDG uptake data were normalized to the mean global cerebral intensity.

2.4. Voxel-based analysis

To evaluate the association between brain metabolism and the serum hormone levels, a voxel-based analysis was performed using the following general linear model:

$$Y = (\text{Hormone}, \text{Age}, \text{Sex}, 1) \times \beta + \varepsilon$$

For each voxel, Y represents the FDG PET signal in each individual patient, Hormone represents the serum cortisol, Age and Sex denote the age and the sex (1 = male, 0 = female) of the patients, respectively, 1 represents the intercept term, β represents the model parameter to be estimated, and ε is the estimated residual. The results were displayed on a template brain at a significance threshold of probability value ($p < 0.05$) and a minimum cluster size of 50 contiguous voxels. The results were then corrected by a permutation test (Chen and Herskovits, 2010) ($n = 1000$) using a randomized ranking of hormone level. The estimated beta values for each hormone were recorded to form a distribution of the regression coefficient. Only voxels with an original p-value less than the 95% p-values based on the permutation test were considered significant.

2.5. Evaluation of the hormone associated brain regions

Based on the method described above, we identified voxel clusters with a significant association between brain metabolism and serum cortisol. The mean normalized metabolism value of the positively and negatively correlated clusters was calculated separately for each patient. Pearson correlation analysis was performed to investigate the association between the serum cortisol and the mean value of the clusters for each patient.

2.6. Statistical analysis

The general linear model and permutation test were performed for voxel-based analysis by using Matlab (R2012a, MathWorks, Natick, MA, USA). Pearson correlation was performed to investigate the association between brain metabolism of the clusters identified by voxel-based analysis and serum cortisol by using Prism (6.0c, GraphPad Software, San Diego, CA, USA). In this study, a p-value of <0.05 indicated a significant difference.

3. Results

3.1. Demographic and clinical data

We systematically reviewed a total of 92 CD patients, 78 of whom had diagnosis of pituitary adenoma confirmed by pathological examination of surgical specimens. Of the patients, 26 (28%) were male and 66 (72%) were female, with a median age of 35 years old (range, 18–65 years old). The mean serum cortisol and serum ACTH levels of the patients were 28.3 μg/dL and 98.3 pg/mL, respectively. The detailed clinical characteristics of the patients are shown in Table 1.

3.2. Voxel-based analysis findings

The anatomical correlation between brain energy metabolism and individual hormone level was identified using voxel-based analysis. Clusters showing a significant association between brain metabolism and serum cortisol levels are shown in Fig. 1. The clusters with a positive correlation between relative FDG uptake and serum cortisol levels were preferentially located in the anteromedial temporal lobe including the hippocampus and amygdala, the insular cortex, and the cerebellum. Meanwhile, the regions where relative brain metabolism was negatively correlated with the serum cortisol levels were mainly in the lateral frontal cortex, medial and posterior occipital cortex, head of the caudate nucleus, and the anterior cingulate gyrus. Allowing to see the inside structures more clearly, we made a rendering image with cutouts (Fig. 2).

3.3. Correlations of hormone level and brain metabolism

The results of correlations between the serum cortisol level and the metabolism of the clusters are shown in Fig. 3. A statistically significant correlation was found between the cortisol level and the mean

Table 1
Clinical characteristics of patients with Cushing's disease ($n = 92$).

Variables	Patients
Number	92
Age	
Median (range)	35 (18–65)
Gender	
Male (%)	26 (28)
Female (%)	66 (72)
Cortisone (μg/dl) (mean ± S.D.)	28.3 ± 10.4
ACTH (pg/ml) (mean ± S.D.)	98.3 ± 80.8

ACTH = adrenocorticotropic hormone.

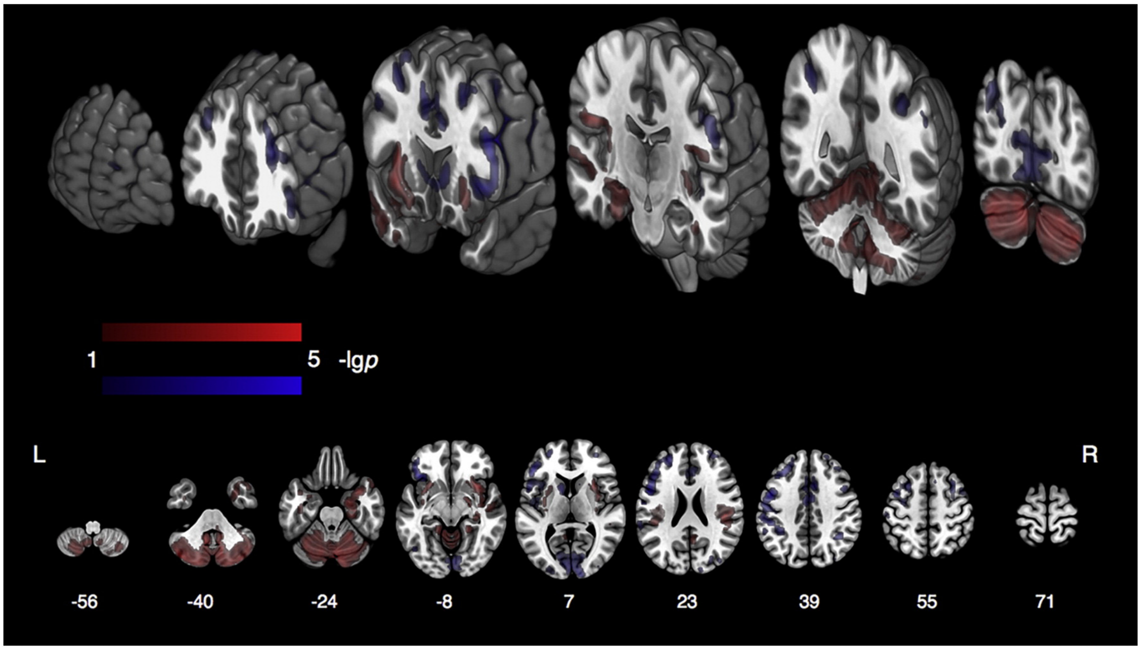

Fig. 1. Coronal and axial slices for the topography of associations between FDG PET measures of brain metabolism and serum cortisol (minimum cluster size = 50 voxels). Brain clusters with significant positive correlations are shown in red color and the negative correlations are in blue. The color range indicates the level of $-\lg p$ ($-\log_{10}p$) value from dark to light.

metabolism value of the positively correlated cluster ($r = 0.436$, $p < 0.0001$) (Fig. 3A). In addition, a significant inverse correlation between the cortisol level and the mean metabolism value of the negatively correlated cluster was found ($r = -0.652$, $p < 0.0001$) (Fig. 3B).

4. Discussion

In this study, we examined the voxel-based association of brain energy metabolism and serum hormone level in patients diagnosed with CD. Notably, we found significant correlations between the individual serum cortisol and the FDG uptake in particular brain regions, including the hippocampus, amygdala, anterior cingulate cortex, and cerebellum, all of which regions have been implicated in the regulation and action of glucocorticoids. Some additional associations between hormone levels and cerebral metabolism were found in the frontal and occipital cortex. Moreover, we examined these clusters for each patient and found good correlations between the FDG uptake and hormone level. These findings provide evidence for functionally relevant associations between brain function and serum level of hormone.

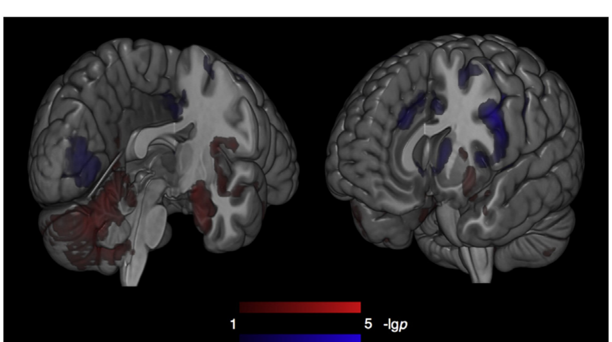

Fig. 2. Rendering images were shown for providing an overall view. The red clusters indicate significant positive correlations and the blue clusters indicate negative. Brain regions associated with the regulation and action of glucocorticoids, specifically, the hippocampus, amygdala, anterior cingulate cortex, and cerebellum are significantly correlated with the serum cortisol levels of patients.

Excessive glucocorticoids affect the morphology and function of the hippocampus, which plays an important role in modulating the activity of the hypothalamic-pituitary-adrenal (HPA) axis via a negative feedback loop involving glucocorticoid binding receptors (Herman et al., 2005; Jacobson and Sapolsky, 1991). Several neuroimaging studies have found that patients with high glucocorticoid levels have a decreased hippocampal volume (Lupien et al., 1998; Starkman et al., 1992), which might be considered an ominous result, implying a risk for cognitive deficits. Indeed, other studies have suggested that elevated cortisol levels are associated with damage to hippocampal glucocorticoid receptors (Sapolsky et al., 1986). In the current study, we explored the association between elevated cortisol level in CD patients and altered brain energy metabolism. Specifically, we found the relative FDG metabolism in the hippocampus to be positively correlated with the patients' serum cortisol level. This correlation may reveal a functional disorder involving hippocampal energy metabolism, and is consistent with the known role of glucocorticoids in modulating uptake and utilization of glucose in the hippocampus (Horner et al., 1990; Virgin et al., 1991).

The neuroimaging findings of hippocampal atrophy do not necessarily imply a permanent loss of neurons. Studies on stress, which involves excessive glucocorticoids, showed conflicting data on hippocampal damages. Studies on rats found glucocorticoids exposure or chronic stress caused a loss of neurons in the hippocampus (Sapolsky, 1985). However, following studies in rodents and non-human primates did not reveal massive neuronal loss or obvious neuropathological changes following glucocorticoids exposure or chronic stress (Pravosudov and Omanska, 2005; Vollmann-Honsdorf et al., 1997). In the current study, the present findings of increased FDG uptake may indicate that the hippocampus is metabolically stressed, instead of neuronal loss, which would likely have resulted in hypometabolism. The atrophy of the hippocampus is likely to be functional disorders rather than permanent damages. Evidence from the clinical practice is after effective treatments, the decreased hippocampal volume associated with sustained hypercortisolemia in CD patients was reversible, at least in part, once cortisol levels decreased (Starkman et al., 1999). A number of subsequent studies likewise found similar hippocampal volume increases after correction of hypercortisolism (Bourdeau et al., 2002; Hook et al., 2007). In addition, the cognitive function of such patients also improved significantly (Hook et al., 2007; Mauri et al., 1993). Apparently, it is

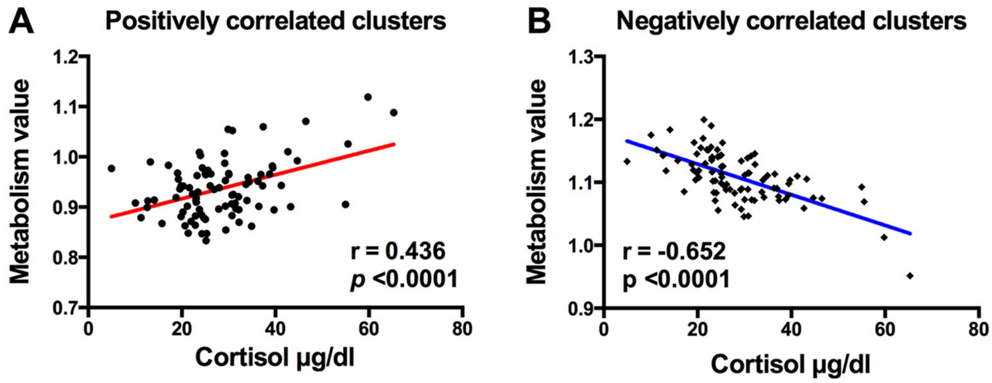

Fig. 3. Correlations of serum cortisol level and brain metabolism value. Pearson analysis was performed between serum cortisol and mean normalized brain metabolism value of the positively/negatively correlated clusters separately for each patient. A, Significant correlation between the cortisol level and metabolism value of the positively correlated cluster ($r = 0.436$, $p < 0.0001$). B, Significant inverse correlation between the cortisol level and metabolism value of the negatively correlated cluster ($r = -0.652$, $p < 0.0001$).

difficult to achieve this recovery depending on the plasticity of the brain. For studies on human beings, it is difficult to get tissues of the brain from patients exposed to excessive glucocorticoids. Our findings, from the view of metabolism of the brain, indicate the possible relationship between hippocampal changes and glucocorticoids exposure.

Other than in the hippocampus, a high expression of glucocorticoid receptors is also characteristic of the amygdala and cerebellum (Hawrylycz et al., 2012). Previous studies have found that the amygdala plays a role in glucocorticoid secretion during stress (Gray et al., 1989), and indeed, a recent functional imaging study in CD patients has demonstrated the occurrence of functional alterations in amygdala (Maheu et al., 2008). Meanwhile, the cerebellum is now understood to participate in cognitive and emotional processes, extending beyond its classical motor functions (Luna-Lario et al., 2011). The cerebellum is also susceptible to increased cortisol levels (Teicher et al., 2003), such that the cerebellar cortex volume is reduced in patients with active CD (Santos et al., 2014). Upon achieving long-term remission, volume increases have been observed in the left posterior lobe of the cerebellum in CD patients (Andela et al., 2013). In the current study, we found that the relative energy metabolism in the amygdala and cerebellum was positively correlated with the serum cortisol level in our CD patients. Based on arguments proposed for our hippocampus findings, we hypothesize that we are seeing metabolic activation that should be rectified upon normalization of serum cortisol levels.

Besides the limbic system and cerebellum mentioned above, the metabolism of the brain neocortex was also perturbed in our CD patients. Previous studies on stress have implicated cortical sites, especially regions in the frontal cortex, to be involved in regulating the HPA-axis activity (Diorio et al., 1993). In addition, recent studies in rats have suggested that the medial frontal cortex and anterior cingulate are involved in glucocorticoid regulation (Sullivan and Gratton, 2002). Accordingly, reduction of the anterior cingulate cortex volume also has been found in animals exposed to hypercortisolism (Cerqueira et al., 2005) as well as in elderly humans with dysregulation of the HPA axis (MacLullich et al., 2006). Moreover, a previous study has demonstrated that the insular cortex is involved in regulating glucocorticoid effects on memory consolidation in rats (Fornari et al., 2012). In the present study, we found that FDG uptake in a number of frontal cortex clusters, specifically including the anterior cingulate cortex and occipital cortex, was negatively associated with the serum cortisol levels. Meanwhile, the FDG uptake in the right insular cortex was positively associated with the serum cortisol levels. These glucocorticoid-associated loci of metabolism in the cortex may generate hypotheses for investigating higher cognitive functional damage in patients with excessive glucocorticoids.

After examining these brain regions from voxel-based analysis, we found the metabolism patterns significantly correlated with serum cortisol levels in CD patients, further demonstrating the association between brain metabolism and the hormone level. In addition, this finding indicates that a consensus of information about brain metabolism may help to evaluate the brain functions and efficacy of treatments in patients with elevated glucocorticoids.

There are several limitations in our study. Due to the exploratory nature of our study, we could not explain all statistically significant associations of regional brain metabolism and hormone levels. We hope that future studies will reveal the specific mechanisms by which these hormones affect brain metabolism. Furthermore, for imaging studies based on voxel-based statistical mapping, registration and normalization procedures present certain caveats. In our study, we completed a more stringent identification of clusters using the permutation test. Finally, for lack of magnetic resonance imaging data in the current study, we could not perform volumetric analysis of the brain regions with metabolic changes associated with serum cortisol. We hope future studies will investigate the structural and metabolic associations of the brain in patients with CD.

In summary, the current study provides quantitative evidence to suggest the association between brain metabolism and plasma level of cortisol in a large series of CD patients. Our findings imply that hormone influences the metabolic activity in specific brain regions, notably those with abundant corticosteroid receptors, and thus will facilitate exploration of the mechanisms of cognitive disorders in patients with abnormal glucocorticoid levels.

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