Altered cerebral Glx concentrations in Cushing's syndrome

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Synopsis

Metabolic alterations were examined by ^{1}H MRS in cerebral areas associated with functional and structural dysfunctions caused by a chronic exposure to glucocorticoids characterizing Cushing's syndrome. A diffuse cerebral reduction of Cho/Cr ratios with an increase of Glx/Cr ratios were demonstrated in the frontal and temporal areas known to be the preferential cerebral targets of excess amounts of glucocorticoids. The Cho and Glx levels could serve as reliable pathophysiological markers of Cushing's syndrome.

Introduction

Cushing's syndrome (CS) is caused either by a long-term endogenous overproduction of cortisol or by the chronic exogenous administration of supraphysiological amounts of glucocorticoids. It has been shown that the hypersecretion of glucocorticoids observed in CS leads to a specific reduction of brain volume in the frontal lobe, cerebellum (1) and hippocampus regions associated with learning and memory deficits (2). Prolonged high levels of cortisol also lead to increased levels of glutamate that binds to NMDA receptors abundant in the hippocampus (3). In a previous ^{1}H MRS study, we demonstrated a statistically significant decrease of Cho in the frontal and thalamic areas of endogenous CS patients (4). The present study aimed at examining Glx alterations in CS patients.

Methods

Forty-one normal subjects were compared to 35 endogenous CS patients. MR spectra were obtained from 2 x 2 x 2 cm^3 ROIs localized in the thalamic, frontal and temporal (including the hippocampus) areas of the left hemisphere. The excitation was performed using the GE PROBE protocol with the STEAM pulse sequence. Acquisition parameters were: TR, 3000 ms; TE, 30 ms; number of acquisitions, 192. Mean NAA/Cr, Cho/Cr, Glx/Cr, mI/Cr metabolite ratios were calculated using the LCmodel software and compared using a two-tailed *t*-test followed by a Bonferroni correction for three areas of measurement with $p<0.017$ (0.05/3) as significance threshold.

Results

CS patients displayed decreased Cho/Cr ratios in the three brain regions, with a statistically significant decrease in the frontal and thalamic areas and a statistical tendency in the temporal area relative to normal subjects (Table 1). In contrast, the Glx/Cr ratios were higher for CS patients in the frontal and temporal areas, with a statistically significant increase in the frontal area. Across all subjects and all regions, Glx/Cr and mI/Cr ratios were positively correlated (r = 0.321-0.488, p = 0.002-0.010).

Table 1. Statistical analysis of differences between groups for metabolite ratios

Brain region	Metabolite ratio	CS Patients	n	Normal subjects	n	*p*-value
Frontal	Cho/Cr	0.270 (0.039)	33	0.301 (0.053)	40	**0.006**
	Glx/Cr	2.000 (0.741)	19	1.563 (0.378)	30	**0.009**
Temporal	Cho/Cr	0.317 (0.058)	33	0.353 (0.074)	38	0.025
	Glx/Cr	2.409 (0.981)	16	2.298 (1.291)	19	ns
Thalamus	Cho/Cr	0.271 (0.044)	35	0.300 (0.048)	41	**0.008**
	Glx/Cr	1.285 (0.260)	31	1.464 (0.353)	35	0.023

Discussion

Considerable evidence now exists that exposure to high levels of cortisol leads to metabolic and structural cerebral changes as well as cognitive dysfunctions. The limbic system (particularly the hippocampus) and cortical areas (particularly the prefrontal cortex) represent significant cerebral targets for the negative feedback actions of circulating cortisol due to their abundant glucocorticoid receptors (3). It has been suggested that excess cortisol increases levels of glutamate, an excitatory neurotransmitter, and leads to hippocampal cell death due to increased neuronal vulnerability to glutamate toxicity (3). The increased Glx levels measured by MRS in the frontal and temporal areas provide new supporting evidence for the role of altered glutamatergic/glutaminergic metabolism in CS. Additionally, the positive correlation between Glx/Cr and mI/Cr levels in the three brain regions could reflect an increased glial activity which is thought to eliminate glutamate from the synapse (5). The reduction of Cho/Cr levels reflect changes in cell membrane metabolism as reported previously (4). Cho and Glx levels may serve as a reliable marker of pathophysiological as well as potential treatment response for CS patients.

References

(1) Negro PJ, et al. *82nd Annual Meeting of The Endocrine Society*, Toronto, Canada, p.466 (abstract 1931), 2000.
(2) Starkman MN, Gebarski SS, Berent S, Schteingart DE. *Biol Psychiatry, 32*: 756-65, 1992.
(3) McEwen BS, Magarinos AM. *Ann N Y Acad Sci, 821*:271-84, 1997.
(4) Khiat A, Bard C, Lacroix A, Rousseau J, Boulanger Y. *NMR Biomed, 12*:357-363, 1999.
(5) Waagepetersen HS, Sonnewald U, Schousboe A. *Neuroscientist,9*:398-403, 2003.