Distribution of neurochemical changes in narcoleptic patients with cataplexy: a proton MR spectroscopy study.

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Introduction

Narcolepsy with cataplexy (NC) is a rare underdiagnosed sleep disorder, characterized by hypersomnia, typically associated with cataplexy (sudden bilateral loss of muscle tone provoked by emotion), disrupted nocturnal sleep and further abnormal REM (Rapid Eye Movement) sleep manifestations [1]. The brain structures interconnected in the regulation of sleep/wakefulness affected in NC are as yet only partially defined. The pathophysiology of NC has been linked to the loss of the hypothalamic hypocretin-containing neurons [2]. Proton MR spectroscopy (^{1}H-MRS) studies have consistently demonstrated a hypothalamic reduction in the neuronal marker N-acetyl-aspartate in NC patients [3,4]. The hypothalamic orexin neurons project to cholinergic structures innervating thalamic nuclei that promote the flow of information to and from the cortex [5]. To date the investigation of thalamus and several cortical regions by various neuroimaging techniques have given contradictory results [6,7]. In the present study of NC patients we used ^{1}H-MRS to look for evidence of neurodegeneration in the hypothalamus, thalamus and parietal-occipital cortex, structures interconnected in the "hypocretin pathway".

Methods

21 Caucasians (mean age 37±17 years), 10 HLA-DQB1*0602-positive NC patients diagnosed according to the International Classification of Sleep Disorders (ICSD) criteria [1] and 10 healthy sex- and age- matched controls were studied using ^{1}H-MRS. All patients suspended medication 20 days before the study. Water-suppressed proton MR spectra were acquired using the PRESS single-voxel localization sequence. Three volumes of interest (VOI) were selected to include: the hypothalamus (volume= 1.0-1.6 cm^3; TR= 1500 ms, TE=40 ms; number of acquisitions=1536); the bilateral medial and posterior thalami (volume=4 to 5.3 cm^3 ,TR= 4000 ms; TE= 35 ms; number of acquisitions= 128); and the midline parieto-occipital cortex (volume= 18 cm^3; TR= 4000 ms, TE=35 ms; number of acquisitions=32), as previous described [3,4]. Metabolite integrals for N-acetyl-aspartate (NAA), creatine-phosphocreatine (Cr), choline-containing compounds (Cho), and myo-inositol (mI) were calculated using the fitting program LC Model [8]. Statistical significance, determined by Student's unpaired *t* test, was taken as $p<0.05$.

Results

All the patients presented normal structural MRI. The results are reported in Table 1. A significant reduction of NAA content, relative to Cr, was found in the hypothalamus of NC patients compared to controls, while Cho/Cr and mI/Cr did not show a statistical difference. On the other hand no significant difference was found in the thalamus and in the parietal-occipital cortex in NAA/Cr, Cho/Cr and mI/Cr in NC patients compared to controls.

Table 1. Hypothalamic, thalamic, and cortical metabolite content relative to creatine from patients and control subjects.

	Hypothalamus			Thalamus			Parieto-occipital cortex		
	NAA/Cr	Cho/Cr	mI/Cr	NAA/Cr	Cho/Cr	mI/Cr	NAA/Cr	Cho/Cr	mI/Cr
Mean±SD	1.35±0.14	0.46±0.09	1.59±0.45	1.32±0.11	0.31±0.03	0.82±0.16	1.41±0.09	0.18±0.02	0.73±0.08
Controls	1.46±0.13	0.46±0.04	1.60±0.26	1.37±0.13	0.31±0.04	0.80±0.16	1.35±0.09	0.19±0.02	0.76±0.10
p	0.02	0.85	0.95	0.32	0.76	0.74	0.12	0.20	0.49

NAA=N-acetyl-aspartate; Cr=creatine; mI=myo-inositol

Conclusions

Our findings suggest that, in NC, the neurodegenerative changes involving primarily the hypothalamus do not lead to neuronal loss or gliosis of the thalamus and of the cortex. Therefore abnormalities showed in these brain regions by PET/ SPECT studies [7,9] are likely to be due to functional changes. The lack of spectroscopic alterations in the thalamus ruled out the presence of thalamic neuronal loss in our patients and is consistent with one report detecting neuropathological alterations confined to the hypothalamus and the pons of a NC subject [10]. Advanced MR techniques may contribute to the clarification of the pathophysiological mechanism of NC, and hence to the development of targeted pharmacological options.

References

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