In vivo evidence of neuronal loss in the hypothalamus of narcoleptic patients

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Introduction

Narcolepsy is a disabling neurological disease affecting approximately 1 in 2000 individuals and characterised by excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, hypnagogic hallucinations, and disturbed nocturnal sleep[1]. Cataplexy, a sudden muscle tone loss brought on by emotions, is a clinical feature almost exclusive to narcolepsy that occurs in around 60% of patients[2]. A dysfunction of the orexin (hypocretin) system in the hypothalamus has recently been linked to the pathogenesis of narcolepsy[3]. Severe reduction in hypothalamic orexin-containing neurons and axons were detected in narcoleptic patients[4]. Conversely, the large majority of narcoleptic patients with cataplexy do not show detectable orexin in their cerebrospinal fluid (CSF)[5]. A recent magnetic resonance study using the voxel-based morphometry technique disclosed a marked bilateral decrease in the hypothalamic grey matter content in narcolepsy patients, not evident on conventional structural MRI[6]. In the present study we used ^{1}H-MRS to look for direct evidence of hypothalamic neurodegeneration in narcolepsy patients.

Methods

We studied 23 patients with narcolepsy (according to the International Classification of Sleep Disorders, ICSD, criteria[1]) (13 males, 10 females; mean age 38 ± 16 SD) with a mean disease course of 16 ± 8 years (range 2 – 22) and 10 healthy subjects (6 males, 4 females; mean age 37 ± 14 SD). Informed consent was obtained from each patient and normal volunteer. Thirteen patients had a typical history of narcolepsy with cataplexy. MR spectroscopy studies were performed in a 1.5T General Electrics Medical Systems (Milwaukee, Wisconsin) Signa Horizon LX whole-body scanner using a 25cm diameter quadrature birdcage head coil. Proton MR spectra were acquired using the PRESS single voxel localisation sequence (TE=40 ms; TR= 1500 ms; number of acquisition = 1536). High resolution images (matrix=256x256; fov = 24x24cm) were obtained by acquiring contiguous 3mm thick axial fast GE (TR= 250m, TE=2.5ms) and sagital Fast SE images (TR=600,TE=12). A voxel (volume ranging from 1 to 1.2 ml) was selected to include bilateral hypothalamic grey matter (Figure 1). Peak area for N-acetylaspartate (NAA) at 2.02 ppm, for creatine-phosphocreatine (Cr) at 3.03 ppm, for choline (Cho) at 3.22 and for myo-inositol at 3.56 were calculated using the time domain fitting program AMARES/MRUI (http://carbon.uab.es/mrui). Peak integral values were expressed relative to the Cr peak. Statistical significance, determined by Mann-Whitney U test and ANOVA, was taken as $p<0.05$.

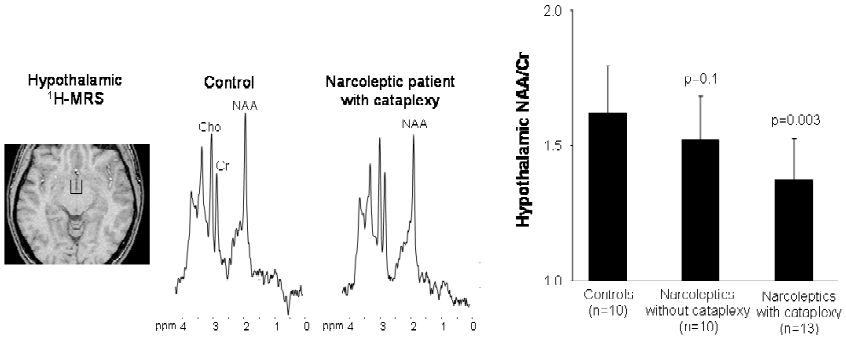

Figure. *Left*: Axial fast GE image showing hypothalamic voxel localisation. *Centre*: Spectra from a healthy volunteer and a patient with narcolepsy. *Right*: mean hypothalamic NAA/Cr in control, and patients with and without cataplexy.

Results

A significant reduction in NAA/Cr was found in the hypothalamus of narcoleptic patients (1.45 ± 0.17, mean ± SD) compared to controls (1.62 ± 0.17; p= 0.013). When dividing our patients into pure narcolepsy (n= 10) and narcolepsy associated with cataplexy (n=13), the hypothalamic NAA/Cr (1.37 ± 0.15) was significantly lower in the narcolepsy with cataplexy patients than in narcoleptics without cataplexy (1.52 ± 0.17; p= 0.03) who, in turn, failed to show a significant hypothalamic NAA/Cr reduction compared to healthy controls (p=0.1) (Figure). Cho and mI to Cr ratios were similar in the hypothalamus of narcoleptic patients and controls (data not shown).

Discussion

NAA/Cr is reduced in the hypothalamus of narcoleptic patients. This neurochemical abnormality is direct evidence that hypothalamic neuronal loss is a pathogenetic feature in narcolepsy. The cause of neuronal loos in narcolepsy is not known. An acute/subacute event (cytotoxic or immunologically mediated), or a neurodegenerative process that becomes clinically evident only when the large majority of orexin-containing neurons is lost could occur. The greater severity of hypothalamic NAA/Cr reduction in patients with narcolepsy with cataplexy compared to those without, adds to the pathological and CSF evidence that these may be two somewhat different conditions. Narcoleptic patients without cataplexy, who presented a mean hypothalamic NAA/Cr lower than that in controls (but not reaching statistical significance), may have a residual number of hypothalamic orexin-containing neurons accounting for the slighter disease severity (marked EDS but no clearcut cataplexy).

References

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