

Introduction

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disease caused by a CAG repeat expansion in the huntingtin gene. Energy metabolism has been a major focus of HD research for many years due to several observations in both patients and models of the disease [1]. Here, our objective was to test the hypothesis that brain energy metabolism is abnormal during brain activation in early-stage HD patients using ^{31}P MRS.

Methods

We studied 15 HD patients at an early stage of the disease and 15 age- and sex-matched controls. All measurements were performed on a Siemens Trio 3T scanner (Siemens, Erlangen, Germany). A 6 cm surface ^{31}P RF coil (Rapid, Rimpar, Germany) was used for ^{31}P transmission and reception. ^1H imaging and shimming were performed with the standard Siemens ^1H body RF coil. ^{31}P -NMR spectra (pulse-acquire, TR = 2s) were measured over 20 min in the visual cortex before, during, and after visual stimulation (4 min rest, 8 min stimulation, 8 min recovery). Spectra were quantified with jMRUI in order to measure the ratios of ATP, phosphocreatine (PCr) and inorganic phosphate (Pi) over time.

Results

In controls, we observed an 11% increase in Pi/PCr ratio ($p=0.012$) and a 13% increase in Pi/ATP ratio ($p=0.008$) during brain activation, presumably reflecting increased ATP synthesis and ADP levels. Subsequently, controls had a return to baseline levels during recovery ($p=0.006$ et 0.011 respectively). In contrast, in HD patients, both Pi/PCr and Pi/ATP ratios remained constant during and after visual stimulation, reflecting reduced mitochondrial activity. In addition, in HD patients the ratio of Pi/ATP correlated with the clinical Unified HD Rating Scale (UHDRS) score during the activation ($r=0.62$, $p=0.014$) and recovery periods ($r=0.65$, $p=0.009$), while Pi/PCr ratio correlated with the UHDRS score during recovery ($r=0.61$, $p=0.016$), reflecting a correlation between brain energy metabolism and disease severity in HD.

Discussion and Conclusion

This is first report of altered brain energy metabolism in HD patients during brain activation. Consistent with a previous report, we saw no change in ^{31}P concentration ratios between controls and HD patients at rest [2]. Previous ^{31}P MRS studies in the normal human visual cortex during visual stimulation gave variable results [3-7]. The excellent SNR and spectral resolution in the present study allowed us to measure relatively small changes in Pi/PCr with high precision and accuracy. In contrast to controls, visual stimulation failed to elicit an increase in Pi/PCr and Pi/ATP ratios in HD patients, suggesting that mitochondrial activity is not adequately stimulated by the task. Although it is a small effect, this reduction in brain energy metabolism can be detected in HD patients at an early stage of the disease. This could provide further insight into cerebral activity in HD, and may provide a new functional biomarker of brain energy deficit to assess therapeutic efficacy in HD in clinical trials.

References

[1] Mochel et al. JCI 121,493, 2011 [2] Hoang et al. Neurology, 50, 1033, 1998 [3] Sappey-Marinier et al. JCBFM 12, 584, 1992 [4] Rango et al. JCBFM 26, 283, 2006 [5] Kato et al. JNCN 8, 417, 1996 [6] Chen et al. MRM 38, 551, 1997 [7] Vidyasagar et al. Exp Brain Res 187, 229, 2008

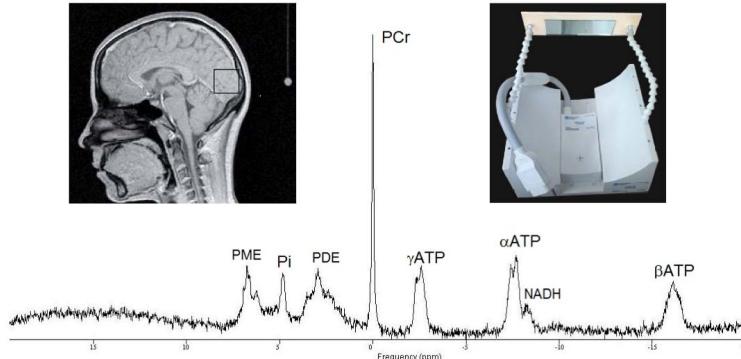


Figure 1. Example of ^{31}P NMR spectrum from the occipital cortex (pulse-acquire, nt 240, TR 2 s). Insets show a ^1H image (left) and a picture of the ^{31}P coil used for ^{31}P MRS (right). A small sphere filled with water, visible on the ^1H image, was placed at the center of the ^{31}P coil and used to verify the position of the ^{31}P next to the visual cortex. The box on the image shows the area used for localized shimming.

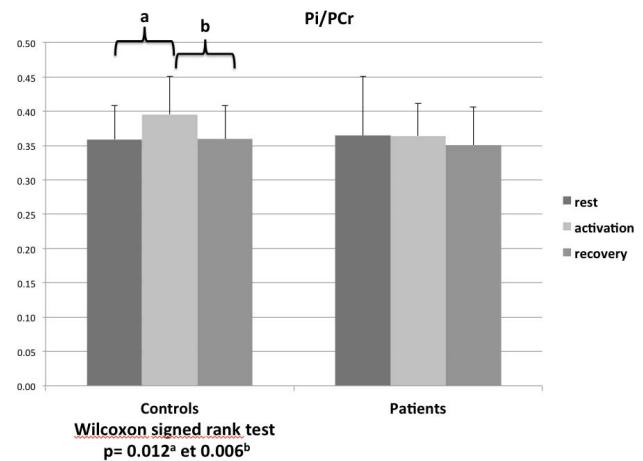


Figure 2. Ratio Pi/PCr in controls and in HD patients during rest, during visual stimulation, and during recovery. Controls showed an increase in Pi/PCr during stimulation, but HD patients showed no increase.