Does visual cortex lactate increase following photic stimulation in migraine without aura patients? A functional $^1$H-MRS study

Harmen Reyngoudt · Koen Paemeleire · Anneloor Dierickx · Benedicte Descamps · Pieter Vandemaele · Yves De Deene · Eric Achten

Received: 10 December 2010 / Accepted: 9 January 2011 / Published online: 8 February 2011 © The Author(s) 2011. This article is published with open access at Springerlink.com

Abstract Proton magnetic resonance spectroscopy ($^1$H-MRS) has been used in a number of studies to assess noninvasively the temporal changes of lactate (Lac) in the activated human brain. Migraine neurobiology involves lack of cortical habituation to repetitive stimuli and a mitochondrial component has been put forward. Our group has recently demonstrated a reduction in the high-energy phosphates adenosine triphosphate (ATP) and phosphocreatine (PCr) in the occipital lobe of migraine without aura (MwoA) patients, at least in a subgroup, in a phosphorus MRS ($^{31}$P-MRS) study. In previous studies, basal Lac levels or photic stimulation (PS)-induced Lac levels were found to be increased in patients with migraine with aura (MwA) and migraine patients with visual symptoms and paraesthesia, paresia and/or dysphasia, respectively. The aim of this study was to perform functional $^1$H-MRS at 3 T in 20 MwoA patients and 20 control subjects. Repetitive visual stimulation was applied using MR-compatible goggles with 8 Hz checkerboard stimulation during 12 min. We did not observe any significant differences in signal integrals, ratios and absolute metabolite concentrations, including Lac, between MwoA patients and controls before PS. Lac also did not increase significantly during and following PS, both for MwoA patients and controls. Subtle Lac changes, smaller than the sensitivity threshold (i.e. estimated at 0.1–0.2 $\mu$mol/g at 3 T), cannot be detected by MRS. Our study does, however, argue against a significant switch to non-aerobic glucose metabolism during long-lasting PS of the visual cortex in MwoA patients.

Keywords Migraine without aura · Functional $^1$H-MRS · Lactate · Visual cortex · Absolute quantification

Introduction

Migraine is a common, disabling, primary headache disorder, with episodic manifestations that affects women three times more than men [1]. Migraine is divided into two major subtypes: migraine without aura (MwoA) and migraine with aura (MwA) [2].

The pathophysiology is still largely unknown despite a surge of interest because of the high prevalence and socioeconomic impact [1]. Subcortical structures, probably including brainstem, hypothalamus and thalamus, are involved in the generation of migraine attacks [3]. Even more puzzling are the mechanisms at the basis of the
interictal brain disorder that predisposes migraine patients to develop an attack. Factors such as genetic background [4–6], nitric oxide hypersensitivity [7], lack of cortical habituation [8, 9], and a disturbed energy metabolism [10] may determine the migraine threshold.

In the last 20 years, several magnetic resonance spectroscopy (MRS) studies have been performed in migraine patients. MRS is a technique to obtain in vivo biochemical information noninvasively. Many of these studies comprised phosphorus MRS ($^{31}$P-MRS) and suggested an interictal energy disturbance in the brain of migraine patients ([10] and references herein). Other studies employed proton MRS ($^{1}$H-MRS) and yielded a lot of heterogeneous, sometimes contradictory, results for metabolites including N-acetylaspartate (NAA: a neuronal marker), total creatine (tCr: a marker of energy metabolism), choline (Cho: a marker for membrane turnover) and myo-inositol (a glial marker) ([11] and references herein). An interesting finding was the elevated interictal level of lactate (Lac) in the occipital visual cortex of a heterogeneous group of migraine patients (i.e., MwA, basilar-type migraine, migrainous infarction) [12], suggesting a deranged oxidative glycolysis. A similar observation was made in four patients with familial hemiplegic migraine (FHM), a rare subtype of MwA [13]. In a functional $^{1}$H-MRS study, photic stimulation (PS) resulted in a Lac increase in the visual cortex of migraine patients with migraine with visual symptoms and paraesthesia, paresia and/or dysphasia, but not in MwA patients, in which Lac was already higher than normal in the resting state [14].

Lac is an interesting metabolite due to its role as an intermediate of glucose metabolism and as a marker of metabolic activity under either aerobic and anaerobic conditions (Fig. 1) [15].

Therefore, the function of Lac during brain activation has been at the centre of brain energy metabolism research [16]. Fox et al. [17] found a mismatch between ΔCMRO$_2$ (variation of cerebral metabolic rate of oxygen), which increased by 5%, and ΔCMR$_{gl}$ (variation of cerebral metabolic rate of glucose) and ΔCBF (variation of cerebral blood flow), which both increased by 30–50% during prolonged neuronal activity in a positron emission tomography (PET) study. Pellerin and Magistretti [18] hypothesized that Lac, and not glucose, was the main metabolic substrate for activated neurons, as part of the so-called astrocyte-neuron Lac shuttle (ANLS). Several $^{1}$H-MRS studies reported an increase in Lac during prolonged PS [19–21]. However, a decrease in Lac was also observed following the presentation of an impulsive PS, partly refuting the ANLS theory [22].

Our group demonstrated a decreased level of high-energy phosphates in the occipital visual cortex of a subgroup of MwoA patients as compared to controls with $^{31}$P-MRS [10]. It was hypothesized that the observed adenosine triphosphate (ATP) is attributed to a reduced aerobic glycolysis and oxidative phosphorylation. This reduction in high-energy phosphates added further evidence to the hypothesis of the presence of a mitochondrial component in the pathophysiology of migraine. The question remained whether there would be an associated switch to anaerobic glycolysis, illustrated by an increase in Lac concentration. A resting state $^{1}$H-MRS study, however, did not show any quantifiable Lac in the visual cortex of the same MwoA patient group as in the $^{31}$P-MRS study [11]. The aim of this study was to investigate potential Lac changes with $^{1}$H-MRS in the occipital visual cortex of MwoA patients as compared to control subjects during and following PS.

**Materials and methods**

**Subjects**

20 MwoA patients (31.9 ± 9.1 years, 3 men) and 20 age- and gender-matched control subjects (31.9 ± 10.3 years, 3 men) were studied with functional $^{1}$H-MRS. All patients were recruited by the local Headache Clinic of the Ghent University Hospital where they were diagnosed with MwoA according to the criteria of the International Headache
Society [2]. On average, patients experienced 3.6 ± 1.1 attacks per month, were not using any prophylactic medication and were attack-free for at least 48 h before the fMRS study. A possible attack after the study was verified by e-mail. The protocol was approved by the local ethics committee and all subjects gave written informed consent.

1H-MRS and photic stimulation

Measurements were performed on a 3 T Siemens Trio Tim whole-body scanner (Erlangen, Germany), using a 26.5-cm-diameter quadrature transmit/receive dual tuned ($^{31}$P, $^1$H) birdcage head coil (Rapid Biomedical, Würzburg-Rimpar, Germany). Spectra were acquired using a single voxel point-resolved spin echo sequence (PRESS), with chemical-shift-selective (CHESS) water suppression. Automatic shimming with manual fine tuning of the $B_0$ magnetic field was used as well as iterative semi-automatic optimization of the transmitter voltage.

The volume of interest (VOI) was placed in the primary visual cortex (Brodmann area 17), centered on the calcarine fissure (Fig. 2a), localized on $T_1$-weighted gradient-echo images in three orthogonal planes with a slice thickness of 1 mm, a repetition time (TR) of 1550 ms and an echo time (TE) of 2.37 ms. VOI size was 20 × 20 × 20 mm$^3$. For each subject, 64 water-suppressed spectra (TE = 288 ms, TR = 2,000 ms, 8 averages), as well as 10 water-unsuppressed spectra at different TE (30, 50, 70, 90, 110, 150, 200, 300, 500, 1,000 ms) and a TR of 10,000 ms (1 average) were acquired. The raw data of each acquisition consisted of 1,024 complex-valued data points, at a sampling period of 0.833 ms. The corresponding bandwidth was 1200 Hz. The total duration of the examination was approximately 40 min.

PS was obtained by the projection of a black-and-white checkerboard, reversing at 8 Hz, and was viewed through MR-compatible goggles. Subjects were instructed to fixate a cross hair in the centre of the reversing checkerboard. The control condition consisted of the projection of a black screen. The

Fig. 2 a Sagittal $T_1$-weighted image with a 20-mm cubic VOI localized in the occipital visual cortex. b MR spectrum of a phantom containing NAA (2.01 ppm) and Lac (1.31 ppm). c Stack plot of spectra obtained before (B), during (stimulation 1, S1 and stimulation 2, S2) and following PS (after, A) in controls. d Stack plot of spectra obtained before (B), during (S1 and S2) and following PS (A) in MwoA patients. In vivo metabolites Lac (1.31 ppm), NAA (2.01 ppm), tCr (3.03 ppm) and Cho (3.19 ppm) are marked in the spectra.
experimental time course was: 6′24″ baseline phase (black screen) corresponding to 16 spectra; 12′48″ on phase (reversing checkerboard) corresponding to 32 spectra; and again 6′24″ baseline phase (black screen) corresponding to 16 spectra.

A phantom was used to evaluate the $^1$H-MRS protocol and contained an aqueous solution of 10 mM NAA and 1 mM Lac (Sigma Aldrich). Sodium azide (NaN$_3$) was added as an antimycotic agent. The phantom was made of plastic, was spherical and had a diameter of 10.4 cm. A spectrum obtained in the phantom is shown in Fig. 2b.

Spectral analysis

Both water-suppressed and water-unsuppressed spectra were recorded in this study.

Water-unsuppressed spectra were processed without apodization and fitted by a single component using Hankel Lanczos Squares Singular Values Decomposition (HLSVD), a method based on the Lanczos algorithm and included in the jMRUI package [24], yielding an estimation of the water signal integral.

In the water-suppressed spectra, the residual water resonance was removed by HLSVD [25]. The signals of Lac, NAA, tCr and Cho were referenced at 1.31, 2.01, 3.03 and 3.19 ppm, respectively (Fig. 2c, d). The spectra were summed and averaged over 16 spectra, according to the corresponding condition. Following apodization (Lorentzian, 5 Hz) and phase correction, the water-suppressed spectra were fitted by the time-domain semi-parametric algorithm QUEST [26], software which is also included in the jMRUI package. QUEST is a non-linear least-squares algorithm that fits a time-domain model function, made up from a basis set of quantum-mechanically simulated whole-metabolite signals. These whole-metabolite signals were simulated with the software package NMR-SCOPE [27], which uses advanced prior knowledge and computes theoretical metabolite signals in terms of spin Hamiltonian parameters [28]. The PRESS sequence was simulated with NMR-SCOPE. Signal basis sets of NAA, tCr, Cho and Lac were created for a TE of 288 ms, so that the $J$-coupling modulations were the same as in vivo. We fitted all metabolites to reduce the effect of the spectral overlap. Each simulated metabolite spectrum was composed of multiple peaks from both the coupled and uncoupled protons.

Quantification

Metabolite ratios of NAA/tCr, Cho/tCr, Lac/tCr and Lac/NAA were calculated using the signal integrals derived with QUEST.

Absolute in vivo concentrations, using the phantom replacement technique with NAA as a reference, were also calculated, using the following equation [29]:

$$[C_i] = \frac{S_i V_i N_i c_{Ti} c_{T2} T_i / P_i c_{load}}{S_r V_r N_r c_{T1} c_{T2} T_r / P_r c_{csf}}$$  \hspace{1cm} (1)

Subscripts $i$ and $r$ correspond with in vivo and the reference phantom, respectively, $[C]$ is the metabolite concentration, the NAA metabolite concentration $[C_i]$ in the reference phantom was 10 mM, $S$ is the signal integral (derived with QUEST), $V$ is the volume of the voxel from which the signal is acquired, $N$ is the number of protons that contribute to the spectral line ($N = 3$ for NAA, tCr and Lac, $N = 9$ for Cho), $c_{T1}$ and $c_{T2}$ are correction factors for the signal loss caused by longitudinal ($T_1$) and transversal ($T_2$) relaxation time, respectively, $T$ is the absolute temperature ($T = 310.16$ K in the volunteer and $T_r = 294.16$ K in the reference phantom), $\rho$ is the density of water, $c_{load}$ is a correction factor that accounts for different coil loading and $c_{csf}$ is the correction factor for partial volume effects, i.e. the fraction of cerebrospinal fluid (CSF) compared to the fraction of water in the brain parenchyma in the VOI. The volume ratio $V_r / V_i$ cancels from the equation since $V$ was the same in the reference phantom and in vivo, i.e. $20 \times 20 \times 20$ mm$^3$. For the calculation of the different correction factors, we refer to a recent publication on quantitative $^1$H-MRS in MwoA [11]. $T_1$ and $T_2$ relaxation times of Lac were derived from another study [30].

Statistical analysis

Statistical analysis was performed using the SPSS software (SPSS 15.0 for Windows; Chicago, IL). Descriptive statistics were calculated for age, gender, signal-to-noise ratio (SNR), signal integral variations, metabolite ratios and absolute metabolite concentrations. To determine whether detectable changes in metabolite ratios and absolute metabolite concentrations occur in MwoA patients as compared to controls, before, during and after PS, a repeated measures ANOVA was performed. The metabolite ratios and concentrations were tested against the hypothesis of within-subject variations (i.e., condition) and between-subject variations (i.e., group). A least significant difference (LSD) test and a Scheffé test were used to evaluate possible group differences. Equality of variances was verified with the Levene’s test and normal distribution of data was evaluated by a Kolmogorov–Smirnov test. Results were considered to be significant for $P < 0.05$.

Results

Spectra obtained during rest and stimulation conditions from both control subjects and MwoA patients are shown in Fig. 2c, d, respectively. Shimming resulted in linewidths around 8 Hz for water.
With the achieved SNR of the summed spectra at a TE of 288 ms, no other peaks than NAA, tCr, Cho and Lac were evident. On average the SNR was identical in the control and MwoA patient group (Table 1). SNR varied around 5% between the resting and stimulation phases (∆SNR).

In a phantom, signal integrals varied from <0.5% for NAA to 1–2% for Lac during the time course of the functional paradigm. Table 2 illustrates the total average in vivo signal integral variation per metabolite, as well as the average variation between the different conditions of the stimulation paradigm. The NAA signal integral has a coefficient of variation (CV) of approximately 3% during the course of the paradigm. For the tCr and the Cho signal, CV has somewhat higher values: around 7 and 11%, respectively. The highest CV, as expected, is found for the small Lac signal integral around 30%. There are no differences between MwoA patients and control subjects for these abovementioned values (P > 0.05). When analyzing the signal integral variation between the three conditions, we observed considerable (for NAA and tCr) to very large (for Cho and Lac) standard deviations.

The evolution of metabolite ratios and absolute concentrations during the stimulation paradigm are shown in Tables 3, 4, respectively. No significant differences in metabolite ratios, including Lac/tCr and Lac/NAA, and absolute metabolite concentrations, including [Lac], were observed between the different conditions in both the MwoA patient and the control group (P > 0.05). Also no significant differences were found between MwoA patients and controls, when looking at separate stimulation conditions (P > 0.05).

**Discussion**

There were several good reasons to perform functional 1H-MRS in the visual cortex of MwoA patients.

The visual cortex is both easily stimulated and an interesting brain region because of its higher energy metabolism. The occipital lobe was found to have a significantly higher regional CMRO₂ as compared to other cortical regions [31], and, according to a PET study, the regional CMRgl was found to be the highest in occipital

### Table 1 SNR

|       | Controls   | MwoA patients |
|-------|------------|---------------|
| SNR   | 2.4 ± 0.37 | 2.4 ± 0.35    |
| ∆SNR (%) | 5.2 ± 2.3 | 5.5 ± 2.5     |

### Table 2 Signal integral variation (%)

| Metabolite | Totala | Controls | MwoA patients | Stimulation — Beforeb | After — Stimulationc | After — Befored |
|------------|--------|----------|---------------|-----------------------|-----------------------|----------------|
| NAA        | 2.9 ± 1.7 | 3.0 ± 1.1 | 1.7 ± 3.3 | 1.3 ± 5.2 | −2.5 ± 4.4 | −1.4 ± 3.5 | −0.8 ± 4.7 | −0.3 ± 4.4 |
| tCr        | 7.3 ± 4.4 | 7.7 ± 4.1 | 4.9 ± 14.4 | 4.5 ± 11.2 | −4.9 ± 10.6 | −0.5 ± 9.8 | −1.4 ± 8.4 | 3.8 ± 14.1 |
| Cho        | 11.9 ± 7.9 | 11.7 ± 7.1 | 8.1 ± 29.5 | −0.3 ± 18.5 | −2.4 ± 16.7 | 1.9 ± 19.5 | 3.1 ± 22.5 | 1.8 ± 28.7 |
| Lac        | 33.4 ± 18.4 | 29.9 ± 17.2 | 16.9 ± 53.1 | 31.4 ± 74.5 | 7.9 ± 86.4 | −5.8 ± 45.5 | 8.3 ± 55.9 | −0.7 ± 42.8 |

a Total reflects the average signal integral variation of all conditions combined (before, during and after PS)
b Signal integral variation of the signals obtained before and during PS
c Signal integral variation of the signals obtained during and following PS
d Signal integral variation of the signals obtained before and following PS

### Table 3 Ratios

| Metabolite | Beforea | Stimulation1 | Stimulation2 | After |
|------------|---------|--------------|--------------|-------|
| NAA/tCr    | Controls | 2.34 ± 0.269 | 2.38 ± 0.289 | 2.26 ± 0.244 | 2.40 ± 0.239 |
|            | MwoA patients | 2.46 ± 0.248 | 2.41 ± 0.233 | 2.42 ± 0.233 | 2.38 ± 0.256 |
| Cho/tCr    | Controls | 0.221 ± 0.061 | 0.236 ± 0.059 | 0.214 ± 0.050 | 0.224 ± 0.036 |
|            | MwoA patients | 0.222 ± 0.059 | 0.228 ± 0.047 | 0.221 ± 0.046 | 0.223 ± 0.045 |
| Lac/tCr    | Controls | 0.242 ± 0.108 | 0.247 ± 0.118 | 0.270 ± 0.118 | 0.243 ± 0.117 |
|            | MwoA patients | 0.267 ± 0.146 | 0.249 ± 0.099 | 0.288 ± 0.127 | 0.258 ± 0.122 |
| Lac/NAA    | Controls | 0.103 ± 0.044 | 0.104 ± 0.048 | 0.120 ± 0.053 | 0.104 ± 0.054 |
|            | MwoA patients | 0.112 ± 0.060 | 0.105 ± 0.043 | 0.126 ± 0.046 | 0.110 ± 0.050 |

a All conditions were averaged over 16 spectra
white matter and the visual cortex [32]. Migraine has been the subject of a large cohort of MRS studies (see reviews in [10, 11]). More specifically, Lac was found to be increased in the visual cortex at rest or following PS of MwA patients and migraine patients with a more complex phenotype (i.e., visual symptoms and one of the following symptoms: paraesthesia, paresia or dysphasia), respectively [12, 13, 14, 33]. A resting state 31P-MRS study in MwoA patients, performed by our group, demonstrated a decrease in high-energy phosphates (ATP and PCr) in the visual cortex, implying a reduction in aerobic metabolism [10]. Furthermore, no quantifiable Lac was observed in the same MwoA patient group, implying there is no significant switch to anaerobic glycolysis in the resting state [11]. The aim of this study was to elucidate whether Lac would increase in MwoA during and following PS.

In the present functional 1H-MRS study we did not observe any significant differences in signal integrals, ratios and absolute metabolite concentrations (including for Lac) between MwoA patients and controls, before PS. These findings are in contrast to observations in three studies covering MwA (including FHM and basilar-type migraine), which reported elevated basal Lac levels [12–14]. The authors of the abovementioned studies suggested that the accumulation of Lac was a marker for a disturbance in oxidative glycolysis, related to energy metabolism impairment, which is typical for mitochondrial diseases [34].

We also did not observe a significant increase of Lac during and following PS, both for MwoA patients and controls. In another comparative fMRS study between patients with MwA and migraine patients with both visual symptoms and paraesthesia, paresia and/or dysphasia (but not MwoA), a PS-induced Lac/NAA increase was reported only in the migraine patients with the more complex phenotype (i.e., visual and other symptoms) while no changes were observed in the MwA and control group [14]. It was postulated that the lack of stimulation-induced Lac increase in MwA and also in patients with mitochondrialopathies might be partially attributed to a saturation of Lac transporter systems [35]. In the subgroup of MwA, with high resting-state [Lac] levels, it was hypothesized that the aura was limited to the visual cortex, whereas in the subgroup of migraine patients with both visual symptoms and paraesthesia, paresia and/or dysphasia, this was not the case. Experiments demonstrated that decreased pH, which would accompany increased extracellular Lac, is an inhibiting factor for cortical spreading depression, which is believed to be associated with the aura symptoms [36]. The lack of a significant increase in Lac in the healthy control population post-PS in our study is in contrast to some other early fMRS studies [19–21], in which PS-induced Lac increases of 60–150% were observed. However, several methodological issues have been raised concerning Lac visibility in MRS as well as Lac dynamics following PS, which are related to low Lac concentrations under different experimental conditions [37, 38]. This led to the need for optimization of the sensitivity and accuracy of fMRS methodology. Mangia et al. [39–41] reported about these issues in several advanced 1H-MRS studies and observed an increase in [Lac] of 0.1–0.2 μmol/g in the first minute of PS, corresponding to an increase of only 20%. In contrast to most previous reports [19, 20, 21, 37, 38], these studies were performed at ultrahigh field strength (i.e., 7 T), resulting in larger chemical shift dispersions and higher SNR compared to lower field strengths. Furthermore, in these studies data were acquired with ultrashort TE and a long TR, minimizing T2 and T1 relaxation effects, and, ultimately leading to very reproducible results with a high SNR. We acquired data using a long TE (i.e., 288 ms) as in several previous fMRS studies [20, 37, 38], resulting in low SNR spectra, large variability in Lac signal amplitudes, and consequently high standard deviations. Lac changes could not be identified at 3 T in the present study in both controls and MwoA patients, as the variations are lower than the sensitivity threshold of 0.1 μmol/g (maximum 0.09 mM, see Table 4), determined in a functional 1H-MRS study in healthy volunteers at 7 T [39]. It should

| Table 4 Absolute concentrations (mM) |
|-------------------------------------|
|                                     |
| [NAA] Controls 14.92 ± 1.39 | 15.05 ± 1.39 | 14.75 ± 1.53 | 14.84 ± 1.70 |
| MwoA patients 15.22 ± 1.76 | 15.36 ± 1.88 | 15.30 ± 1.90 | 15.21 ± 1.80 |
| [tCr] Controls 12.68 ± 1.60 | 12.63 ± 1.69 | 13.14 ± 1.47 | 12.25 ± 1.47 |
| MwoA patients 12.43 ± 1.84 | 12.59 ± 1.84 | 12.54 ± 1.69 | 12.67 ± 1.59 |
| [Cho] Controls 0.88 ± 0.22 | 0.93 ± 0.17 | 0.89 ± 0.21 | 0.88 ± 0.18 |
| MwoA patients 0.92 ± 0.22 | 0.88 ± 0.18 | 0.89 ± 0.17 | 0.90 ± 0.18 |
| [Lac] Controls 0.51 ± 0.19 | 0.53 ± 0.23 | 0.60 ± 0.24 | 0.52 ± 0.24 |
| MwoA patients 0.55 ± 0.29 | 0.60 ± 0.24 | 0.62 ± 0.23 | 0.53 ± 0.26 |

* All conditions were averaged over 16 spectra
also be emphasized that the calculated absolute metabolite concentrations (i.e., around 0.5–0.6 mM) are in the range of what is assumed as normal for healthy brain (i.e., 0.2–1.0 mM); and Lac increases of up to 0.2 mM are unlikely to reflect a switch to anaerobic glycolysis, according to Mangia et al. [40].

In conclusion, we can state that in this study no observable changes in Lac were found in MwoA patients, both at rest and following PS. This is in contrast to observations in MwA patients (and variants) as reported by others. This suggests that the observed Lac increase in previous MRS studies at 1.5 T in MwA is linked to aura, and therefore suggests that the observed Lac increase in previous MRS studies in MwoA patients (and variants) as reported by others. This is in contrast to observations in a homogeneous MwoA patient group, and an age- and gender-matched control group. Our study argues against a significant switch to non-aerobic glucose metabolism during long-lasting PS of the visual cortex of MwoA patients.

Acknowledgments This research is funded by the Special Research Fund PhD-grant (B/07768/02) and performed at GHMI. The Department of Radiotherapy is also greatly acknowledged for the use of the Radiophysics lab.

Conflict of interest None.

Open Access This article is distributed under the terms of the Creative Commons Attribution License which permits any use, distribution and reproduction in any medium, provided the original author(s) and source are credited.

References

1. Edmeads J, Mackell JA (2002) The economic impact of migraine: an analysis of direct and indirect costs. Headache 42(6):501–509
2. The International Headache Society Classification Subcommittee (2004) The International Classification of Headache Disorders, 2nd edn. Cephalalgia 24(S1):1–160
3. Goadsby PJ (2009) Pathophysiology of migraine. Neurol Clin 27(2):335–360
4. Russell MB, Olesen J (1993) The genetics of migraine without aura and migraine with aura. Cephalalgia 13(4):245–248
5. Russell MB, Iselius L, Olesen J (1995) Inheritance of migraine investigated by complex segregation analysis. Hum Genet 96(6):726–730
6. De Vries B, Frants RR, Ferrari MD, Van Den Maagdenberg AM (2009) Molecular genetics of migraine. Hum Genet 126(1):115–132
7. Olesen J (2008) The role of nitric oxide (NO) in migraine, tension-type headache and cluster headache. Pharmacol Ther 120(2):157–171
8. Schoenen J (1994) Pathogenesis of migraine: the biobehavioural and hypoxia theories reconciled. Acta Neurol Belg 94(2):79–86
9. Schoenen J (1998) Cortical electrophysiology in migraine and possible pathogenic implications. Clin Neurosci 5(1):10–17
10. Reygoudt H, Paemeleire K, Descamps B, De Deene Y, Achten E (2011) 31P-MRS demonstrates a reduction in high-energy phosphates in the occipital lobe of migraine without aura patients. Cephalalgia (in press)
11. Reygoudt H, De Deene Y, Descamps B, Paemeleire K, Achten E (2010) 1H-MRS of brain metabolites in migraine without aura: absolute quantification using the phantom replacement technique. Magn Reson Mater Phys 23(4):227–241
12. Watanabe H, Kuwabara T, Okubo M, Tsuji S, Yuasa T (1996) Elevation of cerebral lactate detected by localized 1H-magnetic resonance spectroscopy in migraine during the interictal period. Neurology 47(4):1093–1095
13. Grimaldi D, Tonon C, Cevoli S, Pierangeli G, Malucelli E, Rizzo G, Soriani S, Montagna P, Barbieri L, Lodi R, Cortelli P (2010) Clinical and neuroimaging evidence of interictal cerebellar dysfunction in FH2. Cephalalgia 30(5):552–559
14. Sander PS, Dydak U, Schoenen J, Kollia[s] SS, Hess K, Boesiger P, Agosti RM (2005) MR-spectroscopic imaging during visual stimulation in subgroups of migraine with aura. Cephalalgia 25(7):507–518
15. Siesjo BK (1978) Utilisation of substrates by brain tissues. In: Brain energy metabolism, 1st edn. John Wiley, New York, pp 101–130
16. Schurr A (2006) Lactate: the ultimate cerebral oxidative energy substrate? J Cereb Blood Flow Metab 26(1):142–152
17. Fox PT, Raichle ME, Mintun MA, Dence C (1988) Nonoxidative glucose consumption during focal physiologic neural activity. Science 241(4864):462–464
18. Pellerin L, Magistretti PJ (1994) Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. Proc Natl Acad Sci USA 91(22):10625–10629
19. Prichard J, Rothman D, Novotny E, Petroff O, Kuwabara T, Avison M, Howseman A, Hanstock C, Schulman R (1991) Lactate rise detected by 1H NMR in human visual cortex during physiologic stimulation. Proc Natl Acad Sci USA 88(13):5829–5831
20. Sappey-Marinier D, Calabrese G, Fein G, Hugg JW, Biggins C, Weimer MW (1992) Effect of photic stimulation on human visual cortex lactate and phosphates using 1H and 31P magnetic resonance spectroscopy. J Cereb Blood Flow Metab 12(4):584–592
21. Frahm J, Kruger G, Merboldt KD, Kleinschmidt A (1996) Dynamic uncoupling and recoupling of perfusion and oxidative metabolism during focal brain activation in man. Magn Reson Med 35(2):143–148
22. Mangia S, Garreffa G, Bianciardi M, Giove F, Di Salle F, Maraviglia B (2003) The aerobic brain: lactate decrease at the onset of neural activity. Neuroscience 118(1):7–10
23. Mangia S, Giove F, Bianciardi M, Di Salle F, Garreffa G, Maraviglia B (2003) Issues concerning the construction of a metabolic model for neuronal activation. J Neurosci Res 71(4):463–467
24. Naressi A, Couturier C, Castang I, de Beer R, Graveron-Demilly D (2001) Java-based graphical user interface for MRUI, a software package for quantitation of in vivo/medical magnetic resonance spectroscopy signals. Comput Biol Med 31(4):269–286
25. Landau D, Mastronardi N, Vanhamme L, Van Hecke P, Van Huffel S (2002) Improved Lanczos algorithms for blockbos MRS data quantitation. J Magn Reson 157(2):292–297
26. Ratiney H, Sdika M, Coenradie Y, Cavassila S, van Ormondt D, Maraviglia B (2003) Issues concerning the construction of a metabolic model for neuronal activation. J Neurosci Res 71(4):463–467
27. Graveron-Demilly D, Diop A, Brigueat A, Fenet B (1993) Product-operator algebra for strongly coupled spin systems. J Magn Reson A 101(3):233–239
28. Govindaraju V, Young K, Maudsley AA (2000) Proton NMR chemical shifts and coupling constants for brain metabolites. NMR Biomed 13(3):129–153
29. Tofts PS (2004) Spectroscopy: ^1^H metabolite concentrations. In: Tofts P (ed) Quantitative MRI of the brain: measuring changes caused by disease, edn. John Wiley, Chichester, pp 299–340
30. Kugel H, Roth B, Pillekamp F, Krüger K, Schulte O, von Gontard A, Benz-Bohm G (2003) Proton spectroscopic metabolite signal relaxation times in preterm infants: a prerequisite for quantitative spectroscopy in infant brain. J Magn Reson Imaging 17(6):634–640
31. Ishii K, Sasaki M, Kitagaki H, Sakamoto S, Yamaji S, Maeda K (1996) Regional difference in cerebral blood flow and oxidative metabolism in human cortex. J Nucl Med 37(7):1086–1088
32. Reivich M, Kuhl D, Wolf A, Greenberg J, Phelps M, Idos T, Casella V, Fowler J, Hoffman E, Alavi A, Som P, Sokoloff L (1979) The [18]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. Circ Res 44(1):127–137
33. Sarchielli P, Tarducci R, Preciutti O, Gobbi G, Pelliccioli GP, Stipa G, Alberti A, Capocchi G (2005) Functional ^1^H-MRS findings in migraine patients with and without aura assessed interictally. Neuroimage 24(4):1025–1031
34. Kaufmann P, Shungu DC, Sano MC, Jhung S, Engelstad K, Mitsis E, Mao X, Shanske S, Hirano M, DiMauro S, De Vivo DC (2004) Cerebral lactic acidosis correlates with neurological impairment in MELAS. Neurology 62(8):1297–1302
35. Pellerin L, Pellegrini B, Bittar PG, Charnay Y, Bouras C, Martin JL, Stella N, Magistretti PF (1998) Evidence supporting the existence of an activity-dependent astrocyte-neuron lactate shuttle. Dev Neurosci 20(4-5):291–299
36. Tong CK, Chesler M (2000) Modulation of spreading depression by changes in extracellular pH. J Neurophysiol 84(5):2449–2457
37. Merboldt KD, Bruhn H, Hänicke W, Michaelis T, Frahm J (1992) Decrease of glucose in the human visual cortex during photic stimulation. Magn Reson Med 25(1):187–194
38. Boucard CC, Mostert JP, Cornelissen FW, De Keyser J, Oudkerk M, Sijens PE (2005) Visual stimulation, ^1^H MR spectroscopy and fMRI of the human visual pathways. Eur Radiol 15(1):47–52
39. Mangia S, Tkac I, Gruetter R, Van de Moortele PF, Giove F, Maraviglia B, Ugurbil K (2006) Sensitivity of single-voxel ^1^H-MRS in investigating the metabolism of the activated human visual cortex at T T. Magn Reson Imaging 24(4):343–348
40. Mangia S, Tkac I, Gruetter R, Van de Moortele PF, Maraviglia B, Ugurbil K (2007) Sustained neuronal activation raises oxidative metabolism to a new steady-sate level: evidence from ^1^H NMR spectroscopy in the human visual cortex. J Cereb Blood Flow Metab 27(5):1055–1063
41. Mangia S, Tkac I, Logothetis NK, Gruetter R, Van de Moortele PF, Ugurbil K (2007) Dynamics of lactate concentration and blood oxygen level-dependent effect in the human visual cortex during repeated identical stimuli. J Neurosci Res 85(15):3340–3346