Протон Магнетна резонантна спектроскопија на мозок (^{1}H-MRS) кај пациенти со темпорална епилепсија

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Абстракт

Податоците што се добиваат при снимањето на магнетно резонантната слика (MRI) (Magnetic Resonance Imaging), се користат за добивање MR спектри на голем број соединенија кои што се добиваат во текот на метаболитичките претворби во мозокот(MRI in vivo ^{1}H-MRS). Со помош на оваа неинвазивна метода може да се анализираат определен број соединенија со водородни атоми односно протони како и други јадра коишто може да се анализираат со MRS (Magnetic Resonance Spectroscopy), кои даваат сигнали во MR спектарот.

Цел: Цел е да се прикажат испитувани метаболити со in vivo ^{1}H-MRS и со анализа на спектрите да се пресметаат односите на површините под соодветните пикови, ленти кај следниве метаболити *A*(NAA)/*A*(Cr), *A*(NAA)/*A*(Cho) и *A*(Cho)/*A*(Cr).

Материјал и методи: Беа испитани 5 пациенти (3М/2Ж), од 25-52 год возраст. Сите пациенти со наод за хипокампална склероза каде MRI по секвенца и протокол за епилепсии (spc ir ns cor p2 iso EPI) како и MR спектрите беа снимени со секвенцата CSI SE 135, на Magnetom Essenza Tim (25x8). Спектрите и сликите беа обработувани со софтвер Numaris/4, верзија Syngo MR C 15.

Резултати: Испитувањата беа вршени тоа што беше правена споредба на симетрични воксели на соодветните пикови што должат на испитуваните метаболити од ... вата и десната страна на хипокампалната ... гија. Истите беа поставени точно над лези та од испитуваниот волумен од соодветно ткиво (ROI од анг.region of interest). Потоа анализа на спектрите беше извршена ас нација на пиковите во спектарот и беа и дени пикови од следните метаболити: N (N–ацетил аспарагинска киселина) 2,03-2 ppm; Cr (креатин) фосфокреатин 3,05ppm; лин 3,23 ppm., и беше проценет релативни сооднос помеѓу овие метаболити врз осн на површините под кривите кои се во пр лема концентрација во испитуваното тк (ROI). Исто така беше применето т.н. Ханте во правило.

Заклучок: Дефинитивните резултати оваа спектроскопска анализа покажаа на лена фокална редукција на невронален маркер NAA/ Cr т.е. ^{1}H- MRSI покажа нам вање во односот на интензитетот на нев налниот маркер N-ацетиласпартат/(креа и фосфокреатин) на ледираниот хипокам Анализата со *Хантеровото правило* покаж дека овој агол *е значително намален.* Спо некои последни изледувања овој наод е нификантен до 90% кај пациентите со М-Т

Клучни зборови: Протон Магнетна ре нантна спектроскопија; епилепсија; тем рална епилепсија

ton Magnetic Resonance Spectroscopy of Brain (¹H-MRS) in patient with temporal lobe epilepsy

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stract

The data provided in the recording of a Mag- Resonance Imaging (MRI), is used for ob- ng MR spectra of many compounds obtained ng the metabolic transformation into the n (MRI in vivo ¹H-MRS). This non-invasive nod can analyze a certain number of com- nds with hydrogen atoms or protons and oth- uclei that can be analyzed by MRS (Magnetic nance Spectroscopy), which provide signals R spectrum.

Aim: The aim is to show the studied metab- s in vivo 1H-MRS and by analyzing the spec- o calculate the relations of the areas under respective peaks, strips in the following me- olites *A*(NAA)/*A*(Cr), *A*(NAA)/*A*(Cho) and ho)/*A*(Cr).

Material and methods: 5 patients were ex- ned (3M / 2H) of 25-52 years old. All patients n a diagnosis of hippocampal sclerosis in ch MRI sequence protocol for epilepsy (spc ir cor p2 iso EPI) and MR spectra were record- with the sequence CSI SE 135, the Magnetom enza Tim (25x8). Spectra and images were cessed with the software Numaris / 4 version go MR C 15.

Results: The tests were carried out by comparison of symmetrical peaks corresponding voxels which are attributable to the examined metabolites of the left and right hippocampal region. They were placed directly above the lesion of the test volume of relevant tissue (ROI from English "region of interest"). Then analysis of spectra was carried out to assign peaks in the spectrum and also other peaks were found in the following metabolites: NAA (N-acetyl aspartic acid) 2,03 - 2,04 ppm, Cr (creatine), phosphocreatine 3,05 ppm, choline 3,23 ppm and was calculated relative ratio of these metabolites on the basis of the area under the curves which are in greater concentration in the test tissue (ROI). The Hunter rule was also applied.

Conclusion: Final results of the spectroscopic analysis showed reduced focal reduction of neuronal marker NAA / Cr i.e. ¹H-MRSI showed a decrease in the ratio of intensity of the neuronal marker N-acetilaspartat / (creatine and phosphocreatine) of harmed hippocampus. The analysis by Hunter rule shows that this angle is significantly reduced.

Key words: Proton Magnetic Resonance Spectroscopy; epilepsy; temporal lobe epilepsy

Introduction

The data provided in the recording of a Magnetic Resonance Image (MRI) (from Eng. Magnetic Resonance Imaging) or MR image, used for obtaining MR spectra of many compounds is obtained in the course of metabolic transformation into the brain.

In Table 1, are the most important metabolites that may be determined by means of Magnetic Resonance Spectroscopy, MRS (from Eng. Magnetic Resonance Spectroscopy).

Examined metabolisms and used sequences in MRI and in vivo 1H-MRS

With this non-invasive method, MRS can analyze a certain number of compounds of hydrogen atoms or protons or other nuclei, because they give signals in MR spectrum.

The metabolism of the brain is very compl and takes place through complex chemical mecl anisms where various macroscopic changes o curs in the anatomical structure of the nervou tissue with characteristic cell heterogeneity (2)

It is therefore necessary to develop methoc and approaches for testing of chemical and bic chemical transformation into special anatomica functional or clinical (locations) parts of tissu such as lesions, tumors or other histopatholo ical changes. To obtain adequate data for thes chemical changes, MRS developed various MF sequences of different RF (Radio Frequency) an the magnetic field gradient G at the fixed magnet ic field of the instrument Bo.

In everyday medical practice of radiologist many different sequences are used and therefor

Core		Freq. /1,5 T	Spin	Finding /%
Proton	^{1}H	63,9	1/2	99,98
Phosphorus	^{31}P	25,9	1/2	100,00
Natrium	^{23}Na	16,9	3/2	100,00
Carbon	^{13}C	16,1	1/2	1,1
Deuterium	^{2}D	9,8	1	0,02
Nitrogen	^{15}N	6,5	1/2	0,37
Oxygen	^{17}O	8,7	5/2	0,04
Fluorine	^{17}F	59,8	1/2	100,00
Lithium	^{7}Li	24,9	3/2	92,50

Table 1. Cores active in MRS, spins and frequencies and finding in nature (Barker et al.) (1)

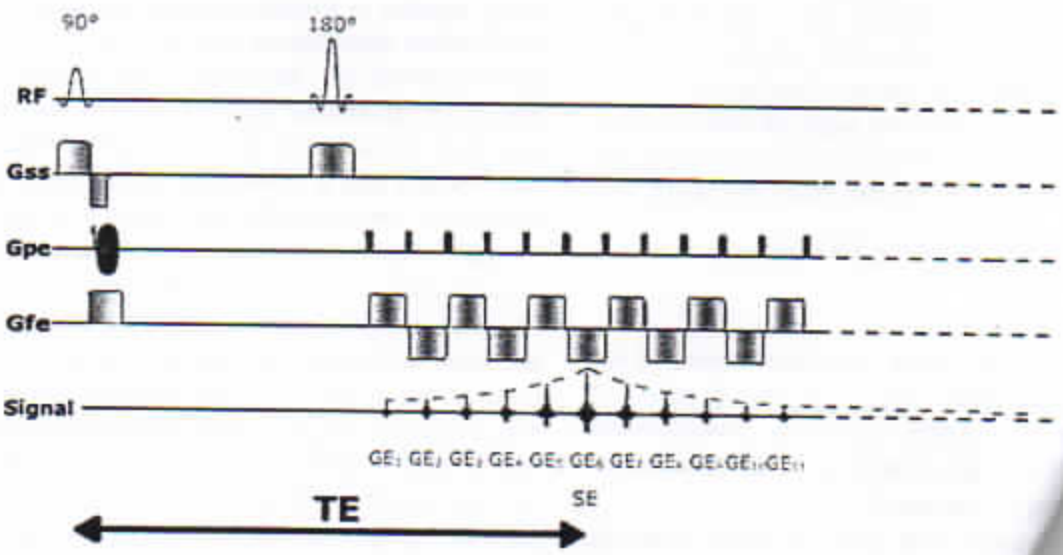


Fig. 1A. Schematic echo planar sequence

portant problem is the standardiza- uences and data collection tools by netic Scanners).

ractice, the literature often encounters equences Point RESolved Spectroscopy S; Bottomley, 1984) (3) and STimulated Acquisition Mode (STEAM; Frahm et al., ') (4).

terial and methods

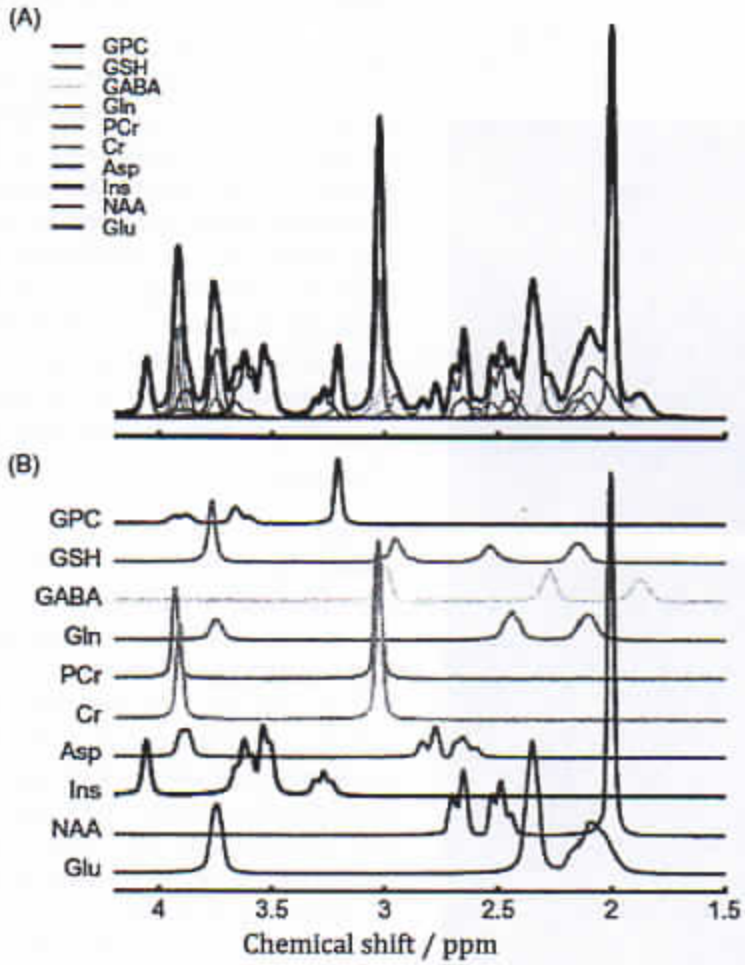
n our work we always used sequence and ocol epilepsies (spc ir ns cor p2 iso EPI), and spectra were recorded with the sequence CSI 35, on *Magnetom Essenza Tim* (25x8).

Fig.1A, presents the standard EPI sequence . Echo Planar Imaging, EPI – which in Sie- s is referred to as EPI SE, i.e. spc_ir_ns_cor_ so_EPI)

For the simplest analysis of MR spectra, the so called Hunter angle is used. It is an angle ght line, which describes the slope of the troscopic profile in MR spectrum of peaks of abolites, which are synthesized in the white er of the brain.

The most common way of analyzing the spectra is to calculate the relationship of the areas under the respective peaks, strips in the following metabolites A (NAA) / A (Cr), A (NAA) / A (Cho) and A (Cho) / A (Cr) . With reference solutions (standards) of known concentration and using standard solutions and analysis phantoms, the absolute concentration of important metabolites in brain tissue can be determined (5).

This technique is known as in vivo Magnetic Resonance Spectroscopy, because it is non-invasive method and it is used for testing of various disorders in the body and in various organs as additional diagnostic method of standard MRI. Measurements can be made to the specific volume whose dimensions can be 2 x 2 x 2. This small volume is known as voxel by analogy to the lowest point in the two-dimensional image, which is known as a pixel. The spectrum that is obtained from the tests is the sum of the separate IR spectra of metabolites in the body that are found in higher concentrations (Fig. 1A).



A. a) Linear combination (sum) of the individual MR spectra of major metabolites are found in the biochemical transformations and b) Separate MR spectra of these metabolites (6)

Fig. 3A. (Patient D.L) MR in range from 0 to 4,5 ppm, 1,5T.

Results

Studied metabolites in vivo ^{1}H-MRS

N-acetyl aspartate

The molecular structure of this compound is given in Table 1. After the water this is most prevalent compound and because if this it occurs most often as the most intensive peak in the MR spectrum of nervous tissue as a single peak in about 2 ppm (Fig.1A), this intense peak due to three hydrogen nuclei of the acetyl methyl group of the NAA. In addition, a careful analysis of the spectrum shows and other peaks derived from this compound and about 2, 49 and 2, 67 ppm. For NAA is often considered that is a marker for active nerve tissue (Meyerhoff et al. 1993) (7). But, there are many cases where the level of NAA shows the change of condition of the nervous tissue (Clark 1998; Gasparovic et al. 2001) (8,9).

Otherwise, NAA is synthesized from aspartate to acetyl-CoA by a reaction catalyzed by aspartate N-acetyltransferase (10). The analysis of the results of previous studies show that there is still no agreement on the subcellular location of this compound in the brain and around the physiological role of NAA.

However, there is general agreement that primarily synthesized in the mitochondria, i precursors found in mitochondria and therefo it is assumed that this compound is synthesize in neuronal mitochondria, although there is i formation that can be found in their cytoplasr There are many other facts that are unexplaine and that can be found in a number of synoptic a ticles of this metabolite (11).

Similar to many trials of metabolites using i vivo 1H-MRS, in all examined patients this m tabolite gives most intense peak of 2,02 ppm.(Ta ble 1)

Creatine and phosphocreatine

Together with creatine and phosphocreatin give remarkable peak at about 3,03 ppm (Fig 2A). This peak is due to the three hydrogen nucle of methyl group of creatine or phosphocreatine Often observed another peak at about 3,94 ppm This singlet derives from metile hydrogen atom of creatine group (Govindaraju et al. 2000) (12 Because of the similar structure of these com pounds, occurs overlapping of their peaks an therefore the strip about 3,03 ppm is assigned a amount of absorption of protons and of the cre atine and phosphocreatine.

Analysis of MR spectra of metabolites

All above indicated parameters, principle and knowledge in the actual moment, 5 patient were examined (3M/2F) of 25-52 years old. Al patients with a diagnosis of hippocampal sclero sis the MRI sequence and epilepsy protocol (sp ir ns cor p2 iso EPI) and MR spectra were record ed with the sequence CSI SE 135, the Magneton Essenza Tim (25x8). Spectra and images were processed with the software Numaris / 4 versior Syngo MR C 15. First, the assignation was made by the most characteristic peaks typical MR spec tra in tested patients.

The tests were carried out by comparison o symmetrical peaks corresponding voxels that are attributable to the examined metabolites left and right hippocampal region. They were placed di rectly above the lesion of the test volume of the relevant tissue (ROI from Eng. region of interest) The voxel positioned just above mesial tempora lobe to cover big part of the hippocampus in a b to avoid partial-volume effects of surround structures, including the amygdala, cerebra id and parahypocampal gyrus. With the F transform, the output signal (FID) transla an appropriate MR spectrum.

Then by analysis of spectra, the a

the spectrum was carried out. The re found by the following metabolites: -acetyl aspartic acid) 2,03-2,04 ppm; Cr ne) phosphocreatine 3,05ppm; choline ppm., and relative ratio of these metabolites calculated on the basis of the area under the rves which are in greater concentration in the it tissue (ROI).

iscussion

Studies show that creatine and phosphocreine are found in white and in gray matter and all types of tissues of the brain parenchyma, cluding to neurons, astrocytes and oligodenocytes. Although in the past it was believed at the content of creatine and phosphocreatine the brain had been due to supply through the ood from other organs, the new findings sugst that there is a possibility of local synthesis these compounds involved with local synthe- in energy metabolism (13) of the nervous tise of the brain. For other aspects of these comunds has a number of new data discussed in eat overview paper of J. Maddock and Michael Buonocore (11).

ompounds of choline

Many different merged into brain tissue ntain polyatomic residue (group) of choline. ne hydrogen atoms choline residue that are rt of the structure of the trimethyl ammonin group consisting of trimethyl groups with ree hydrogen atoms, give an intense peak at out 3,21 ppm. In brain cells, the phosphoryl oline (PCho) and glicero phosphoryl choline PCho) are the primary sources of this intense ak. The joined components are phospholipids the component and myelin membranes of the ain parenchyma cell (Boulanger et al. 2000) 4). Other derivatives of the brain membranes ve lower concentrations and therefore cannot detected by this type of MR spectra. Because these features, peaks that are observed in the ectra represent an indicator of the changes in cell membranes of brain tissue. The increased intensity of the peaks of choline is considered an indicator for the accumulation of breakdown products of myelenic shell, which occurs during intensive or active demyelination (Yue et al. 2009) (15).

The results of the relative ratios of the concentrations of metabolites are given in Tables 4. The so-called Hunter rule was also applied (Alexander Lin, 2005) (16).

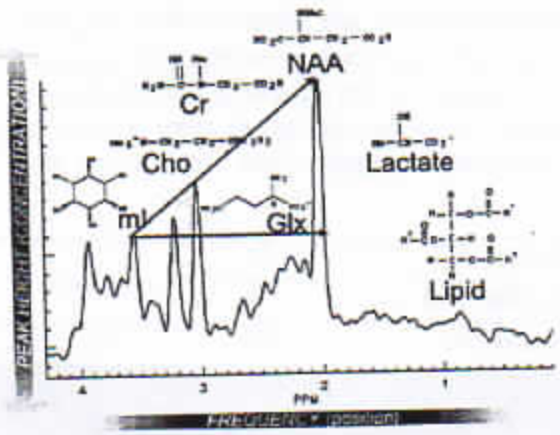


Fig. 4A. Graphic display of normal MRS in white matter of the brain and of the Hunter angle (16)

Ratio of the reference metabolite NAA / Cr is made. Reference metabolite has a value 1 and the ratio of the areas is compared in terms of the concentration of this metabolite (2).

ble 2. in vivo MRS of a voxel in a patient with hippocampal (left).

tabolite	δ /ppm	Height of the pick	Half-width of the pick	A
AA	2,02	1,72	4,10	7,49
	3,04	1,17	4,10	5,10
o	3,22	1,21	3,70	4,78
2	3,93	0,52	5,00	4,10

Chemical shift; A - Peak area

Table 3. in vivo MRS of a voxel in a patient with hippocampal (right).

Metabolite	δ /ppm	Height of the pick	Half-width of the pick	A
NAA	2,02	1,39	4,90	6,85
Cr	3,04	0,89	5,00	4,75
Cho	3,22	0,96	4,90	5,02
Cr2	3,93	0,56	10,80	9,53

δ – Chemical shift; A - Peak area

The table below shows the relative relation between the areas of signals due to major metabolites:

Table 4. Normal and pathological values of the relation areas to major metabolite

Relative relation of the surfaces*	Normal value	Pathological value
A(NAA)/A(Cr)	2,0	<1,6
A(NAA)/A(Cho)	1,6	<1,2
A(Cho)/ A(Cr)	1,2	>1,5

*-According to: (http://spinwarp.ucsd.edu/neuroweb/Text/mrs-TXT.htm)

Table 5. Normal, pathological values and determined relative ratio of the areas to major metabolites in tested cases

Relative relation of the surfaces*	Normal value	Pathological value	Specific value
A(NAA)/A(Cr)	2,0	<1,6	1,44
A(NAA)/A(Cho)	1,6	<1,2	1,36
A(Cho)/ A(Cr)	1,2	>1,5	1,05

Moreover, the application of Hunter rule indicates that the angle is less than 45 °.

Table 6. Normal, pathological values and certain relation surfaces of some important metabolites in tested cases.

Relative relation of the surfaces*	Normal value	Pathological value	Specific value
A(NAA)/A(Cr)	2,0	<1,6	1,47
A(NAA)/A(Cho)	1,6	<1,2	1,57
A(Cho)/ A(Cr)	1,2	>1,5	0,94

The calculated ratio of the areas in the appropriate metabolites are lower than normal. It relates primarily to the relation *A*(NAA)/*A*(Cr) of the peak areas of N-acetyl aspartate and creatine.

Final results of the spectroscopic analysis showed reduced focal reduction of neuronal marker NAA/Cr i.e. 1H-MRSI showed a decrease in the ratio of intensity of the neuronal marker N-acetyl aspartate/(creatine and creatine phosphate) of affected hippocampus. Moreover, the analysis with Hunter rule shows that this angle (Fig. 4A) is significantly reduced. According to some recent investigations, this finding is significant to 90% in patients with TLE M (17).

Conclusion

Final results of the spectroscopic analysis showed reduced focal reduction of neuronal marker NAA/Cr i.e. ^{1}H-MRSI showed a decrease in the ratio of intensity of the neuronal marker N-acetilaspartat/(creatine and phosphocreatine) of harmed hippocampus. The analysis by Hunter rule shows that this angle is significantly reduced. Metabolic spectroscopic investigation, which was conducted as an additional test method is undoubted proof factor to confirm the lesion wi loss of pyramidal cells in M-TLE.

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