Cerebral Lactate Detected by Regional Proton Magnetic Resonance Spectroscopy in a Patient With Cerebral Infarction

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Water-suppressed image-guided localized proton magnetic resonance spectroscopy was performed in a 59-year-old woman with two major brain infarcts. Spectra were measured in the infarcts, in an area between the infarcts, and in the healthy hemisphere. The volumes of interest were selected on the basis of a fast T2-weighted image. A 1331-2662 Hahn spin-echo sequence was used to suppress the water in the 8-cm³ volume that was selected by means of spatially resolved spectroscopy or stimulated echoes. The spectra were obtained in 5 minutes' accumulation time. Spectral editing was applied to separate the resonance of lactate from that of other substances. Our results show no increase of lactate concentration within the infarcts after 6 months; however, a resonance was observed at 1.6 ppm, which is assigned to fatty acids. Peak intensities of brain-specific compounds were decreased. Six months after the onset of clinical symptoms (at the time of bypass surgery), a fivefold increase in lactate concentration compared with normal values was observed in the area between the two infarcts. Four months after bypass surgery, the lactate concentration in this area had decreased to only twice normal. We speculate that lactate is a marker of reversible or impending brain damage. (Stroke 1988;19:1556–1560)

In vivo metabolic studies of cerebral ischemia in patients have become possible with the introduction of positron emission tomography (PET).¹ Oxygen consumption, related to adenosine triphosphate (ATP) production, can be measured by means of PET. Magnetic resonance spectroscopy (MRS) can be used to obtain even more basic information about in vivo tissue metabolism.² It is of great importance that not only function, blood flow, and anatomic structures, but also tissue metabolism, can be studied in vivo. Better understanding of the pathophysiologic mechanism may have implications for clinical treatment. The potential of MRS for metabolic studies of the brain has been recognized for several years. Animal studies have demonstrated that after hypoxia or ischemia, energy-rich phosphate (ATP and phosphocreatine [PCr])³ concentrations and tissue pH decrease while intracellular phosphate (Pi) and lactate concentrations increase.⁴⁻⁶ Recently, technical developments have made it possible to extend phosphorus-31 MRS to the examination of patients. It is now possible to obtain well-defined localized spectra from the human brain using image-selected in vivo spectroscopy (ISIS).⁷⁻⁸ The first studies using phosphorus-31 MRS in infants with birth asphyxia indicated that the PCr/Pi ratio could be used to predict clinical outcome.⁹ Recent studies of chronic infarction conclude that the ratios of phosphorus-containing metabolites are not sensitive indicators of functional impairment in chronic brain infarction in adults.⁷ However, a decrease of up to 40% in the total phosphorus signal of infarcted tissue was observed. A decrease of ATP and PCr concentrations in the acute stage leads to an increase in Pi concentration, thereby changing the PCr/Pi ratio. The disappearance of total phosphorus in the chronic stage indicates tissue loss or that tissue with high phosphate concentrations has been replaced by tissue with low phosphate contents. These results indicate that changes in total phosphate concentration reflect irreversible brain damage. From proton MRS in animals, it is known that lactate concentration increases simultaneously with changes in energy-rich phosphate concentration after occlusion of major cerebral blood vessels or after hypoxia.⁵⁻⁶ The question remains whether lactate concentration can be elevated without the implication of irreversible brain damage.
in vivo is more complicated than phosphorus MRS due to two major complicating factors. First, to observe metabolites with an intracellular concentration of 1-10 mM, it is necessary to suppress the water signal, which is approximately 10,000 times as great. From high-resolution proton MRS, several pulse sequences are known to suppress the water signal.10 Second, in general only small areas are involved in pathologic processes. Spatial localization is therefore of foremost importance to obtain proton spectra from infarcts or tumors. Since lipid signals from subcutaneous fat tissue and bone marrow overlap those of interesting metabolites such as lactate, localization techniques are necessary to suppress these unwanted signals by at least a factor of 1,000. We discuss results obtained by different image-based localization techniques in a study of regional brain metabolism, present preliminary results obtained in a patient with a 6-month history of cerebral ischemia, and discuss the significance of water-suppressed proton MRS in humans.

Subject and Methods

Localized proton magnetic resonance spectra were obtained with techniques that use switched magnetic gradients to obtain signals from well-defined volumes of the human brain. The volumes of interest (VOIs) were selected from a proton nuclear magnetic resonance image using a multiple slice sequence (repetition time = 300 msec, echo time = 30 msec). All measurements were performed using a 1.5-T Philips Gyroscan imager (Best, The Netherlands) and a standard headcoil. Spectroscopy was performed using exactly the same hardware configuration as for imaging; therefore, spectroscopy immediately followed imaging, absolutely guaranteeing that the spectra could be assigned to the VOI indicated on the images. Localized shimming was done by monitoring the water signal from the VOI chosen for spectroscopy. Typical line width achieved was 0.1 ppm. After shimming, the carrier frequency was readjusted to the resonance of water; thus, shimming did not affect the location of the VOI. To suppress the intense water signal, binomial excitation sequences10 were used in combination with selective presaturation pulses. Signals from subcutaneous fat and bone marrow in the skull were suppressed by volume selection.

Two different localization schemes were used on different examinations. First, a spectrum was obtained before bypass surgery using the spatially resolved spectroscopy (SPARS) sequence.11-13 The bandwidth of the selection pulses was 650 Hz and the echo time was 136 msec to edit the spectrum using the scheme described by Williams et al.14 This sequence preserves magnetization in the VOI whereas all signals from outside the VOI are destroyed. The sequence can easily be combined with an editing technique by which the lactate signal can be discriminated from those of other compounds that may resonate at the same frequency.14 This editing sequence employs the fact that coupled spins (as in lactate) can be either positive or negative, depending on the selectivity of the 180° refocusing pulse in an echo sequence. Such a sequence is necessary to confirm that the measured signal arises from lactate and not some unsuppressed lipid from the surroundings.

During the second examination, after bypass surgery, a different localizing scheme was used by which spectra from three different regions could be measured during the same examination. The sequence used for these latter examinations is derived from the stimulated echo (STE) technique,15 which was extended with the water-suppression techniques mentioned above.

A 59-year-old woman with a 6-month history of paresis of her left arm and a left-sided hemianopsia was referred to our clinic because of gradual deterioration of the paresis over the previous few months. A computed tomogram (CT scan) showed two infarcted areas, one in the left middle cerebral artery (MCA) territory and the other in the watershed territory between the left MCA and the posterior cerebral artery. An angiogram showed subtotal occlusion of the left internal carotid artery at the siphon. Nuclear magnetic resonance images showed that T1 and T2 were prolonged in the infarcted areas. Between these two infarcted areas was a third area with only minor changes in T1 and T2. Technetium scintigraphy performed in the acute stage showed an intact blood-brain barrier in this third area. Water-suppressed proton magnetic resonance spectra were obtained from the three VOIs shown on the T2 transverse image in Figure 1. One VOI was centered between the two infarcts, one in an infarcted region, and the third in the unaffected contralateral hemisphere.

Results

Water-suppressed proton magnetic resonance spectra from the brain of a normal volunteer obtained at 1.5 T show resonances that can be assigned to phosphocholine (PCh), PCR/creatine, N-acetyl-aspartate (NAA), and lactate (Figure 2). In normal volunteers lactate concentrations were 0.5-1 mM. Using the SPARS technique, spectra were obtained from an 8-cm3 volume with a 1331-2662 sequence for water suppression. This was followed by a second experiment using a 1331-180 block-pulse for editing.14 After subtraction, the lactate resonance was observed at 1.3 ppm in the edited spectrum, as described in "Subject and Methods." This signal has been assigned to lactic acid on the basis of its chemical shift and because its J-modulation is that expected for lactic acid. Alanine and threonine have similar chemical shifts and J-modulations. Biochemical measurements in animal experiments have revealed that lactate accumulates during cerebral infarction. Figure 3 shows the results of the same measurements in the 59-year-old patient, obtained from Area 1 in Figure 1, between the two infarcts. Assuming a normal lactate concentration of 1 mM,
FIGURE 1. $T_2$-weighted nuclear magnetic resonance image after bypass surgery in 59-year-old woman, showing $3 \times 3 \times 3$ cm volumes of interest from which spectra in Figure 4 were obtained. 1, between two infarcts; 2, in infarcted area; 3, in contralateral hemisphere.

the local lactate level was calculated to be 5–10 mM. The patient was operated upon and received a superficial temporal artery-to-MCA bypass. There was no change apparent in the nuclear magnetic resonance images, and her clinical signs and symptoms remained unchanged.

Four months after surgery a second spectroscopic examination of the patient was performed. A localization technique based on the STE technique was used to select VOIs. This second study revealed a decrease in the signals from PCh, PCr, and NAA in Area 2 (Figures 1 and 4). Resonance was observed at 1.6 ppm, which is tentatively assigned to lipids. In Area 1, there still was an increase in lactate concentration, but to only twice normal values, those in the contralateral hemisphere (Figures 1 and 4). There was no significant change in the other signals. The spectrum obtained from Area 3 showed no abnormalities (Figures 1 and 4).

Discussion

Our results indicate that water-suppressed image-guided localized proton MRS can be successfully used to examine patients with cerebral infarction. Imaging takes no more than approximately 5 minutes. For each VOI, it is necessary to perform localized shimming. Acquisition of spectra from a 8-cm$^3$ volume is possible in 5 minutes using the

headcoil for emission and detection of the radiofrequency signal. The entire procedure takes 45–60 minutes to examine two VOIs. Because we used a headcoil, we could position the VOI within any region of the brain. The VOI can be reduced to 1 cm$^3$ with, however, an important loss of the signal-to-noise ratio. Spectroscopic localization methods, such as SPARS and STE, allow selection of VOIs by using principles based on imaging. Thus, the location and size of the VOI is determined with the accuracy of the image by using appropriate selection gradients and selection pulse bandwidths. The profile of the VOI is determined by the shape of the selection pulse; we used 5-G pulses.

In this patient, as well as in other patients with established infarcts, no increase in lactate concentration was observed in the infarct; however, the proton spectrum showed definite abnormalities. There was a decrease in all the signals that can be observed in normal brain tissue (PCh, PCr, NAA). The observed resonance at 1.6 ppm supposedly reflects an increase in lipid or protein concentration in gliotic scar tissue. In this patient, an increase in lactate concentration was observed in the area between two infarcts, an area that on hemodynamic grounds can be suspected to have marginal perfu-
sion (the so-called penumbra). The results of our follow-up study indicate that an increase in lactate concentration does not necessarily mean that the area becomes necrotic. A decrease in lactate concentration after bypass was observed; however, it is not known how the metabolic alterations would have evolved if surgery had not been undertaken. If this area had been partially infarcted after the initial increase in lactate concentration, we could expect to find some of the same changes as in the infarcted region. From our follow-up, it is obvious that the increase in lactate concentration did not result in infarction. It can be concluded that lactate production is reversible in this area of marginal perfusion. It is tempting to speculate that lactate is an indicator of reversible or impending brain damage. There is some evidence from animal studies that a small increase in lactate concentration does not change the ATP, PCr, and Pi concentrations or pH in a model of marginal ischemia. If no cells die, metabolic alterations can be expected to be fully reversible, and no structural changes will be observed on nuclear magnetic resonance imaging. It is, however, still doubtful whether a chronic penumbra exists. Our results show that water-suppressed localized proton MRS can now be used to examine abnormal cerebral metabolism in patients. Proton MRS provides the possibility of studying acute metabolic effects as well as the evolution over time of ischemia. Lactate, which is generally considered to be harmful for brain tissue, is a most important metabolite, which can be observed in the proton spectrum. Our results indicate that in chronic ischemia, lactate concentration can be elevated in the area around the infarct. Changes within the infarct differed from those in the surrounding tissue. Therefore, it seems that proton MRS is a more sensitive indicator of chronic infarction than phosphorus MRS.

More studies are necessary to validate our observation that lactate may be an indicator of impending brain damage. Simultaneous studies of energy metabolism and lactate accumulation, combining phosphorus and proton MRS, may help to answer this question.

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