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In vivo NMR Imaging of Tissue Sodium in the Intact Cat before and after Acute Cerebral Stroke

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The first in vivo nuclear magnetic resonance (NMR) images of tissue sodium in the intact animal are presented. The distribution of sodium in the normal cat's head is described. An experimental stroke was surgically induced. Sodium NMR imaging showed a pronounced focal increase in cerebral sodium concentration 9 hr after ligation of the middle cerebral artery. The method appears to be very sensitive for early detection of infarction. The measured increase in the regional sodium NMR signal probably reflects both a true increase in concentration of brain sodium and an increased NMR visibility of the sodium nucleus in the region of the infarction.

All in vivo nuclear magnetic resonance (NMR) imaging of the intact animal has thus far been limited to proton NMR. The single previous attempt at imaging sodium involved a heart surrounded by saline solution in a perfusion apparatus [1]. The purpose of the present study was to investigate the feasibility and usefulness of in vivo sodium imaging.

Sodium is present primarily in the extracellular space. It is expelled from the intracellular space by the adenosine triphosphate (ATP) pump. Extracellular sodium concentration is 0.145 M, while intracellular sodium concentration is 0.012 M. Total sodium concentration in brain tissue is 0.05 M. Pathologic changes that result in expansion of the extracellular space or impairment of the sodium pump will cause an increase in sodium concentration in the tissue. Tissue injury, edema, or necrosis leads to a remarkable increase in sodium level. Experiments in the cat [2, 3] have demonstrated a 10% increase in water and 300%–400% increase in sodium concentration in the first day after cerebral infarction. Sodium concentration continues to increase, reaching a peak of 600% on the fourth day after ligation of the middle cerebral artery. This pronounced elevation in the relative concentration of sodium prompted the present investigation.

Materials and Methods

We used the transorbital approach, described by O'Brien and Waltz [4], for occluding the middle cerebral artery of the cat. The vessel was either ligated or cauterized at a point lateral to the optic chiasm as it enters the sylvian fissure. Surgery was performed with the operating microscope under sterile conditions. The dura was left open at the conclusion of the procedure. After complete hemostasis in the orbit had been assured, the orbital cavity was partially packed with sterile gauze and eyelids were sutured shut.

The experimental NMR scanner developed at Columbia University features a superconducting magnet (Intermagnetics General Corp.) with a 30 cm wide bore capable of achieving a 30 kG magnetic field. The imaging area is 12 cm in diameter. We used three-dimensional Fourier imaging with a spin-echo scanning sequence for all experiments. The repetition rate was 100 msec for sodium and 250 msec for proton. The radiofrequency was maintained at 30 MHz for both nuclei. The magnet was operated at about 27 kG for sodium and about 7 kG for proton. Sodium imaging was achieved with a 32×32 data acquisition in 3.5 hr. Proton imaging was achieved with either a 64×64 or 128×128 data acquisition set over a period of 0.5 hr. The spatial resolution in the sodium images is estimated at 2.5 mm^3 and the resolution in the proton images is estimated to be about 0.9 $mm.^3$ Four normal control cats were imaged to study the sodium distribution in the normal cat's head. Sodium imaging was attempted in several experimentally infarcted cats but, for technical reasons, the infarctions could not be imaged early enough in all models. In two cats, however, the infarction was seen in the acute phase.

Results

Proton NMR Images in the Normal Cat

The proton NMR images of the normal cat's head are displayed in figure 1. The series of 16 images represents 16 axial sections extending caudad from the level of the anterior orbital cavity to the neck below the foramen magnum. The cat is supine. This set of images is presented to serve as an anatomical guideline for the sodium images, which were taken with the cat in the same position.

Sodium NMR Images in the Normal Cat

Very little sodium is present in the normal brain. Only the eyes and the cerebrospinal fluid in the basal cisterns contain enough sodium to provide a recognizable image (fig. 2). The eyes (frames 3–8) appear as bright spheres because of the large amount of extracellular fluid in the aqueous and vitreous chambers. The lens appears as a central defect in the sodium-containing sphere because it contains a lower concentration of sodium. Intracranially, the cerebrospinal fluid appears as a triangular density representing

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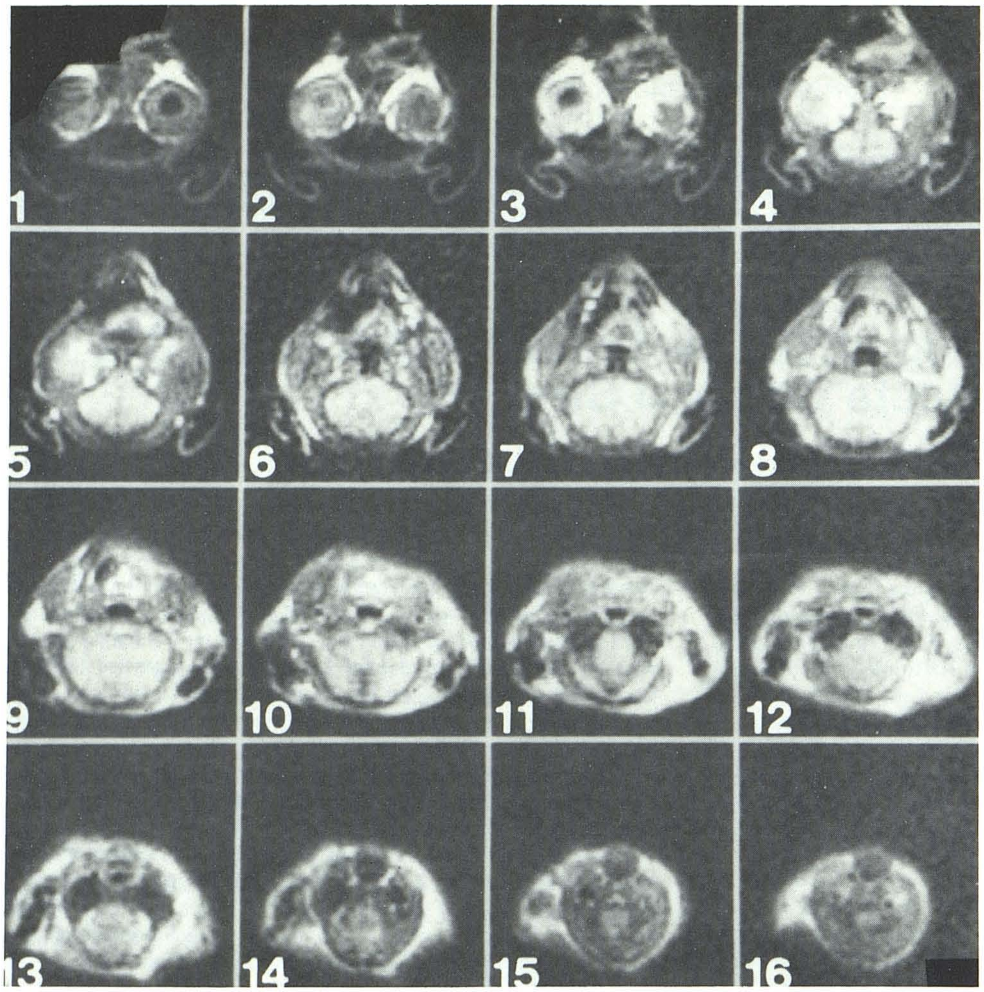


Fig. 1.—Proton NMR images. Normal cat's head, cat supine. Axial sections progress caudad from level of anterior orbital cavity to neck below foramen magnum. Frames 1–3: eyes and orbital fat. Frame 5: frontal pole of brain. Frame 8: parietal lobes.

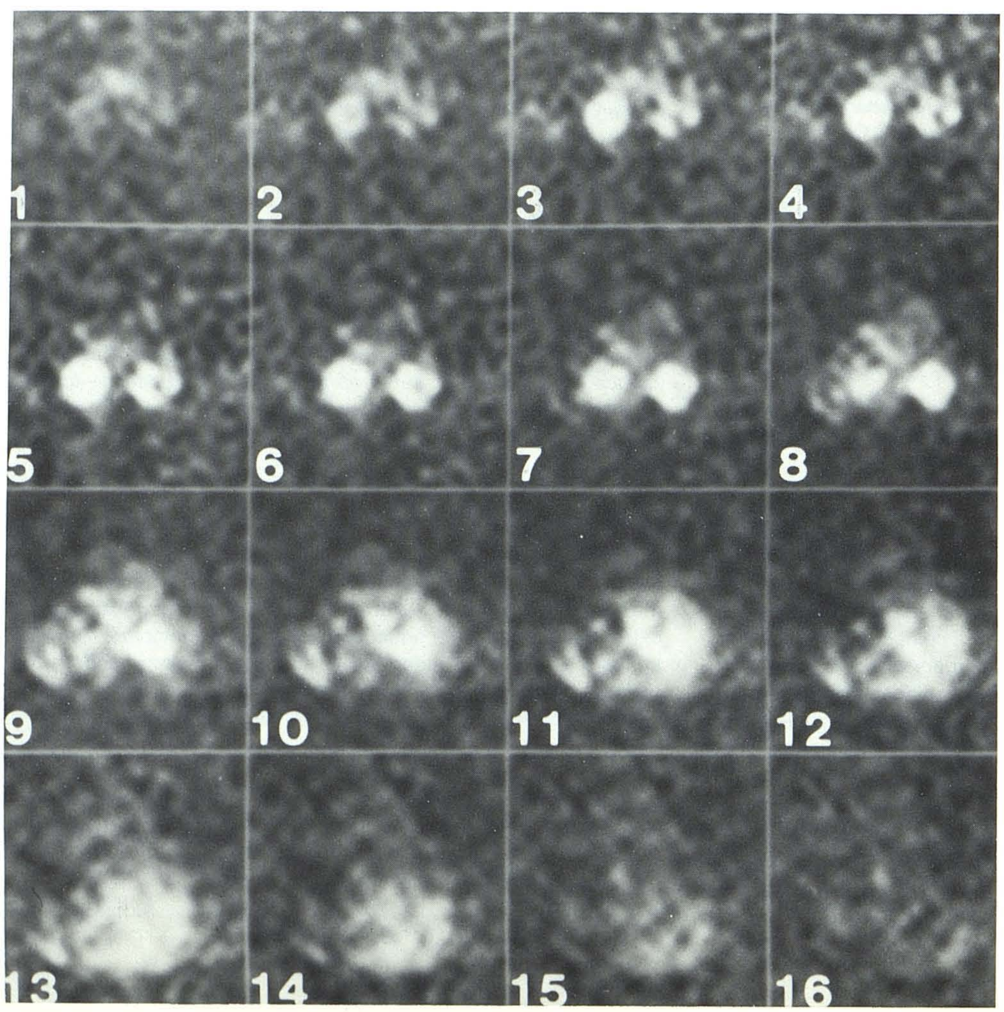
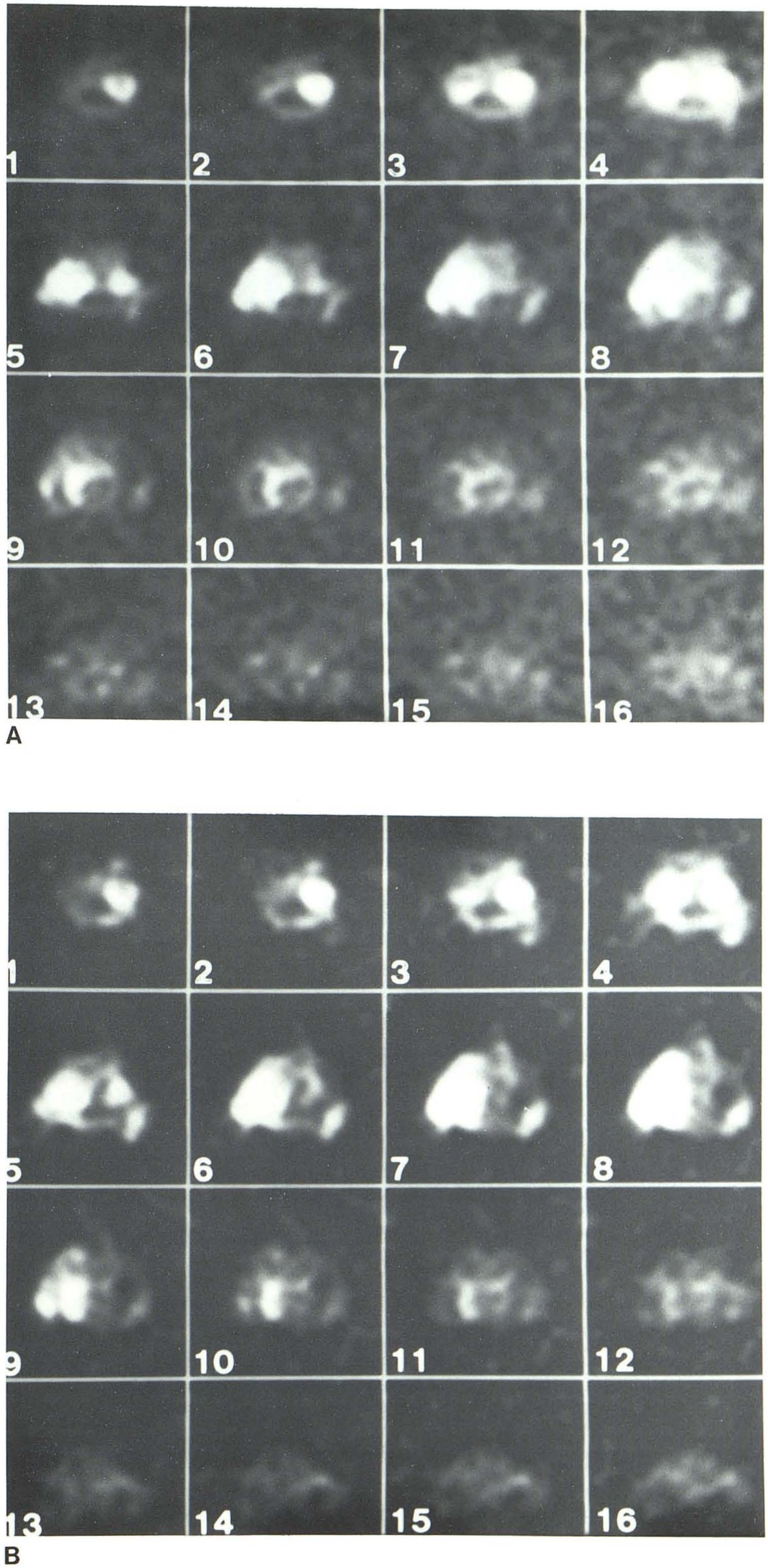
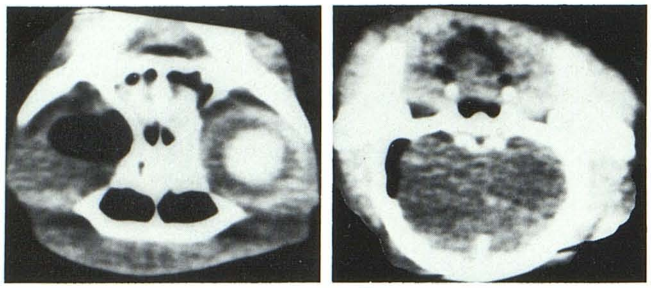


Fig. 2.—Sodium NMR images. Normal cat's head. Frames 3–8: eyes. Frame 12, triangular outline: basal cisterns containing cerebrospinal fluid. Slight increase in signal on left side of head is due to technical reasons and not related to sodium concentration.

Fig. 3.—Sodium NMR images. Infarcted cat. **A**, 9 hr after ligation of middle cerebral artery. Frame 3 shows fluid level in right orbit. Frame 8, marked increase in sodium signal from right cerebral hemisphere. Circular density in frame 11 represents cerebrospinal fluid in perimesencephalic cistern. **B**, 13 hr postinfarction. Increase in size of infarction of right cerebral hemisphere with midline shift to left.





4A 4B

5

Fig. 4.—X-ray CT scan. Infarcted cat, 14 hr after ligation of middle cerebral artery. **A**, Section through orbital cavities. Right orbit shows fluid level as in fig. 3A, frame 3. **B**, Section through cerebral hemispheres. No discernible difference in density between normal and infarcted hemispheres.

Fig. 5.—Proton NMR image. Infarcted cat, 24 hr postinfarction. Slight loss of gray- and white-matter contrast in right cerebral hemisphere as compared with left. Ventricles are shifted to left.

the cisterns surrounding the brainstem and upper part of the cerebellum near the tentorial incisura (frames 12 and 13). A minimal amount of sodium is seen in the soft tissues outside the skull. The NMR sodium signal, measured from the images, is four times stronger in the eye than in the muscle or brain. By chemical measurement, the sodium concentration in the eye (as in the cerebrospinal fluid) is about three times that of the brain and muscle tissue. The discrepancy between the two measurements could be due to various factors, including image noise. We suggest, however, that a greater proportion of eye sodium than brain sodium is NMR-visible.

Sodium NMR Images in the Stroke Model

The first set of sodium images in the stroke model (fig. 3A) was obtained about 9 hr after surgery. A normal eye is seen in the proper location in the left orbit and has, as usual, a round shape. The right orbit contains exudate and cerebrospinal fluid. A very bright sodium signal originating in the right cerebral hemisphere reflects a marked focal increase in sodium concentration. An estimate of the sodium concentration may be obtained from the images by comparing the density of the infarcted brain with that of the globe. This suggests a higher concentration of sodium in the infarcted brain than in the serum exudate of the right orbit or the intraocular humors. Since the concentration of sodium in the infarction cannot exceed that of the serum, it is suggested that more of the sodium in the infarcted brain has become NMR-visible. The second set of images (fig. 3B), obtained 13 hr after surgery, shows an increase in the size of the infarction. The average sodium concentration, however, appears to have remained the same. One can see a shift of the midline to the left side.

X-ray CT in the Stroke Model

The same cat illustrated in figure 3 was examined by x-ray computed tomography (CT) (fig. 4). As in the sodium NMR images, the right orbit shows a fluid level (fig. 4A). As expected, the CT scan of the brain (fig. 4B) shows little difference in density between the two hemispheres. This is not unusual in a 14-hr postinfarction CT scan.

Proton NMR Images in the Stroke Model

Proton NMR images of the infarcted cat's head were obtained about 24 hr after surgery (fig. 5). The ventricles appear shifted from right to left and there is a marginally perceptible loss of gray- and white-matter contrast in the right cerebral hemisphere as compared with the left. The minimal change in proton density is in keeping with previous laboratory results in the experimental stroke model, which demonstrated only a 5%–10% change in water content in the region of the stroke 12 hr after vascular occlusion.

Discussion

Detection of the NMR signal from the sodium nucleus is difficult. For the same magnetic field and the same number of nuclei, the sensitivity of NMR for sodium is only 6% that for protons. Further increasing the difficulty is the low concentration of sodium in the tissues. While proton concentration in water is 110 M, the sodium concentration is only 0.16 M in plasma and even less in brain tissue (estimated at about 0.05 M). Moreover, only 40% of the sodium in living tissue is NMR-visible [5, 6]. For in vivo NMR imaging using the same magnetic field as protons, the signal obtained from sodium is about 4,000 times weaker than that of protons. In our experimental design we enhanced the sodium signal by increasing the magnetic field from 7 kG to 27 kG, thus imaging both nuclei at 30 MHz; by increasing the number of signal averages, taking advantage of the short T_1 of sodium; and by relaxing the spatial resolution for the sodium images as compared with proton images.

We have presented the first in vivo NMR images of tissue sodium in the intact animal, using both normal and surgically infarcted cats. The in vivo sodium NMR imaging confirmed previous experimental data [2, 3, 7] which reported a 200%–400% increase in sodium concentration in the infarction. In our experiments, an increase in the sodium concentration was detected as early as 9 hr after the ligation of the middle cerebral artery; we suspect that if the imaging had been performed earlier, the change in sodium concentration would have been detected at an even shorter interval after surgery. The increased sodium signal from the infarcted hemisphere is stronger than the signal from the serum or from the eye, suggesting that a greater proportion of the sodium in the infarcted brain is NMR-visible than in normal tissues. By comparison, the postinfarction changes seen on the proton images are much more subtle. Sodium NMR imaging appears to offer a very sensitive technique for the early detection of infarction and concomitant tissue damage. The reasons for the increased sodium signal from the infarcted brain are complex and seem to reflect both an actual increase in sodium concentration and an increased sodium visibility.

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