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The Effect of Phospholipid Vesicles on the NMR Relaxation of Water: An Explanation for the MR Appearance of the Neurohypophysis?

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The normal neurohypophysis is hyperintense relative to brain and adenohypophysis on T1-weighted MR images, but the signal is not chemically shifted with respect to water. The source of the hyperintense MR signal in the normal neurohypophysis has been the subject of recent controversy. To date, an adequate biophysical explanation for the unusual imaging properties of the neurohypophysis has not been found. The purpose of this study was to investigate the effect of two chemical components of the neurohypophysis, phospholipids and vasopressin, on the MR signal. We synthesized phospholipid vesicles of the same size as those found in the neurohypophysis (100–200 nm) and quantitatively measured T1, T2, and chemical shift in a spectrometer at concentrations of 0–250 mg/ml of phospholipid. Imaging of the test materials was performed on a 1.5-T whole-body MR system using T1-weighted images, T2-weighted images, reduced bandwidth, and fat suppression techniques. The experiment was also performed with saline buffer, mineral oil, vasopressin, and vasopressin incorporated into the core of the phospholipid vesicles. We found that a solution containing phospholipid vesicles has T1 and T2 characteristics analogous to the neurohypophysis and that this solution exhibits a *single* peak that is not chemically shifted with respect to water. Vasopressin had no effect on the signal, neither in solution nor in the vesicles.

We conclude that phospholipid acts as a relaxation enhancer of water protons and that the MR characteristics of the phospholipid vesicles can account for the observed MR properties of the neurohypophysis.

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The MR signal of the posterior pituitary gland is unique among neural tissues. It is markedly hyperintense relative to brain on T1-weighted spin-echo (SE) images, a characteristic usually associated with subcutaneous and bone marrow fat, not neural tissue. Yet, on T2-weighted SE images, the neurohypophysis is brighter than subcutaneous and bone marrow fat [1], indicating that it possesses a longer T2 relaxation than fat, and it does not have the typical 3 parts per million (ppm) chemical shift relative to the water proton resonance that is associated with most lipid proton resonances [2–6]. These findings are not easily explained by the MR relaxation and spectral characteristics of lipids, neural tissue, or other constituents of the posterior lobe.

There has been considerable interest in elucidating the cause of this hyperintense signal because of its apparent association with the neurosecretion of vasopressin, a hormone synthesized in the hypothalamus and stored in the neurohypophysis [7–10]. Several groups of researchers have shown that the signal is absent in states of vasopressin depletion, both in humans and in animals [6–10]. While it is attractive to speculate that vasopressin or its neurophysin carrier protein is responsible for the signal [6, 7, 10], we know of no biophysical mechanism by which these materials can account for the marked T1 shortening observed in the neurohypophysis at the concentrations at which they are found in this tissue.

We have previously investigated the relationship of intracellular lipids to this signal [9]. Although the biological role of lipids in the posterior lobe is poorly

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understood, an association between the amount of lipid present in pituicytes and the magnitude of the hyperintensity of the signal has been demonstrated in an animal model [9]. However, several studies have now shown that the signal is not chemically shifted with respect to the water proton resonance and thus the causal role of lipids with respect to the signal, if any, is not straightforward, or, as some have suggested, not tenable at all [4–6]. Although neither vasopressin nor lipids can at first impression be invoked as the direct source of the hyperintense signal, this study demonstrates that phospholipids satisfy two fundamental criteria required for an adequate explanation of the observed MR phenomenon: phospholipids are associated with the neurosecretory process, and they can induce a short T1 and an intermediate T2 in the water signal without either shifting the resonance frequency of the water or giving rise to any detectable lipid resonance.

It was the purpose of our investigation to study the effect of phospholipid vesicles (liposomes) on the NMR signal in vitro and compare it with that of the neurohypophysis. Phospholipids are found in relatively high concentration in the neurohypophysis, forming the main constituent of the axonal membrane, the membrane surrounding the neurosecretory granule, and are also found within the pituicytes. In this study we demonstrate that, in vitro, the MR characteristics of suspensions of phospholipid vesicles are the same as those of the posterior lobe of the pituitary gland.

Materials and Methods

A phantom was constructed of small cylindrical tubes filled with a standard saline solution, mineral oil, a concentrated solution of vasopressin (0.2 mg vasopressin/ml buffer), suspensions of phospholipid vesicles in the standard saline solution (at two different concentrations of phospholipid), and a suspension of phospholipid vesicles into which vasopressin had been incorporated into the aqueous core.

The standard saline solution consisted of phosphate buffered saline (PBS) doped with manganese chloride (0.12 mmol/1) to create an aqueous solution with relaxation times approximating that of the adenohypophysis. It was necessary to dope the PBS with a paramagnetic agent to create a reference solution with relaxation times approximately the same as the reference tissue, the adenohypophysis. Undoped PBS had T1 > 2000 msec and T2 > 200 msec and was not suitable for this purpose. Manganese chloride was used as the doping agent because manganese-doped buffer better approximated the T1 and T2 of the adenohypophysis than did copper sulphate. This solution of Mn^{2+}-doped PBS (Mn-PBS) was used as an external reference standard throughout the study.

Relaxation Measurements and Spectroscopy

A suspension of phospholipid vesicles (liposomes) with an aqueous core of Mn-PBS was synthesized from egg phosphotidylcholine (lecithin) with mean vesicle sizes of 112 nanometers (±30 nm) at a concentration of 250 mg of lecithin/ml of Mn-PBS [11]. Serial dilutions of the liposome preparation yielded samples of liposome suspension ranging from 0 to 250 mg of lecithin/ml of Mn-PBS. The T1 relaxation, T2 relaxation, and NMR spectral chemical shift were measured for each of the liposome suspensions on a spectrometer operating at 1.5 T (Bruker, W. Germany). The procedure was repeated for each of the test materials in the phantom. T1 was measured by repeated inversion recovery at TR = 5000 msec and TI increments of 20 msec with 100 points and 10 averages. T2 was measured by a Carr-Purcell-Mieboom-Gill sequence at 500/5 (TR/TE), with 100 points and 10 averages.

MR Imaging

In the second part of this experiment the phantom was imaged alongside the head of three normal volunteers in an axial or sagittal plane through the neurohypophysis. The pulse sequences used were T1-weighted (500/20) SE proton density and T2-weighted (2000/35,70) SE reduced bandwidth (±6 kHz to create a fat-water shift of 8 pixels), and fat suppression. A hybrid method was used for fat suppression. This involved presaturation by means of a 1331 rf pulse followed by the Dixon method. Spoiler gradients were applied immediately after the 1331 pulse in the x, y, and z directions to dephase the magnetization of the suppressed component in the transverse plane. The 180° refocusing pulse was positioned at or shifted from the center between the 90° pulse and the sampling window for the acquisition of the in-plane and out-of-plane signal, respectively, which are then added together [12]. All imaging was at 1.5 T. The intensity and shift of each of the vials were assessed relative to the neurohypophysis and to each other.

Results

Relaxation Measurements and Spectroscopy

The T1 and T2 relaxation times of the test materials are listed in Table 1. Serial dilutions of the phospholipid preparation demonstrated a concentration-dependent relationship between phospholipid concentration and T1 and T2 relaxation (Fig. 1).

The most significant features of these measurements are that there is a significant shortening of relaxation times (increased relaxivity) induced by the liposomes as the phospholipid concentration increases. For example, T1 decreases by approximately 10% at a phospholipid concentration of 20 mg/ml. At higher concentrations (>60 mg/ml) T1 approaches that of mineral oil but T2 remains considerably longer, a behavior

TABLE 1: Relaxation Times and Spectroscopy (Mean Values with Standard Deviations)

Test Material	T1 (msec)	T2 (msec)	Shift (ppm)[a]
Mineral oil	350 ± 2	45 ± 2	3.4
PBS	818 ± 14	175 ± 3	0
Vasopressin[b] (in PBS)	814 ± 20	168 ± 3	0
Vasopressin[c] (in vesicles)	520 ± 3	185 ± 2	0
Phospholipid (50 mg/ml)	518 ± 4	148 ± 1	0
Phospholipid (150 mg/ml)	267 ± 1	100 ± 1	0

Note.—PBS = phosphate buffered saline.

[a] Shift relative to PBS.

[b] 0.2 mg vasopressin/ml PBS.

[c] 0.2 mg vasopressin solution in vesicles, vesicle concentration = 50 mg phospholipid/ml PBS.

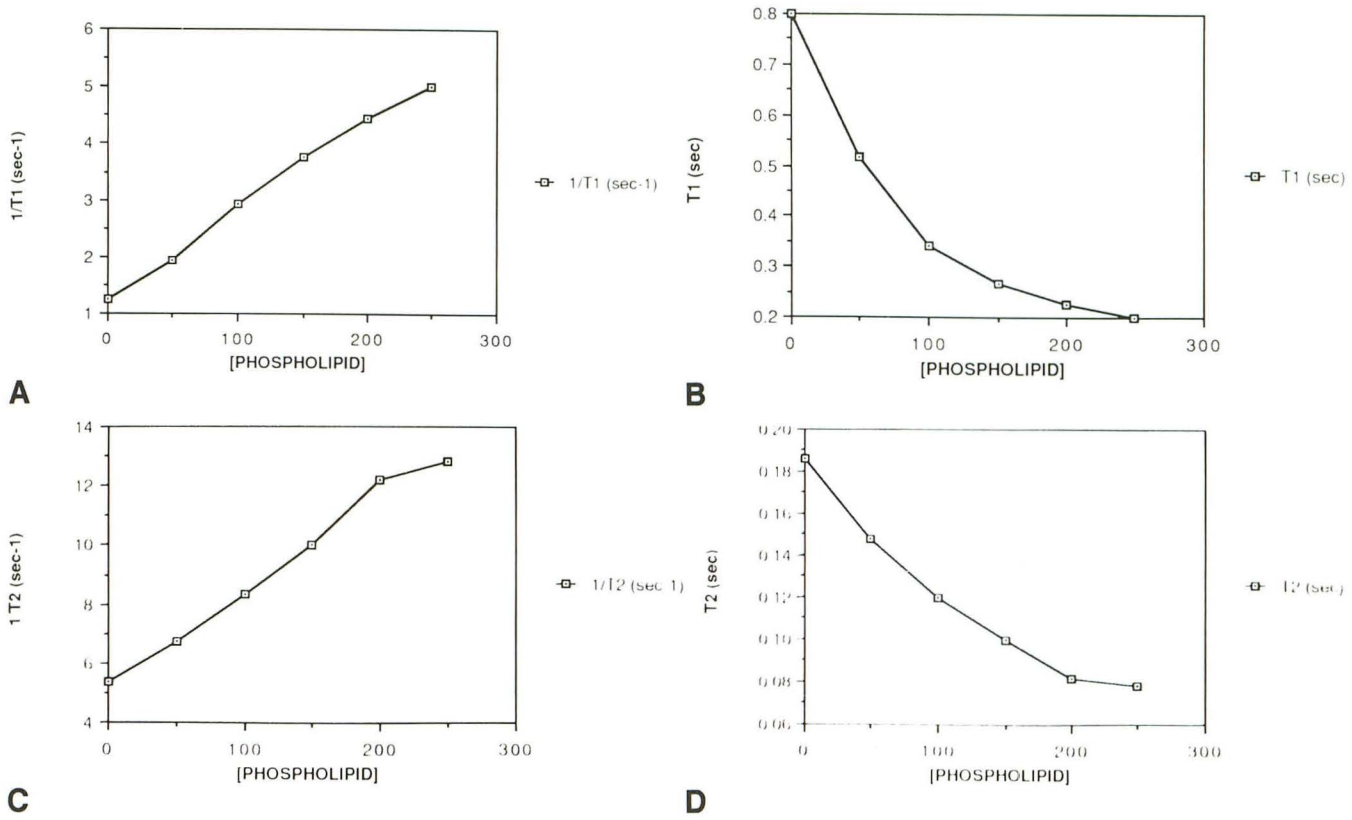

Fig. 1.—*A*, T1 relaxivity (1/sec) as a function of phospholipid concentration (mg/ml). T1 relaxivity is linearly dependent on phospholipid concentration (r = 1.00) over the entire range tested (0–250 mg/ml).

B, T1 relaxation (sec) as a function of phospholipid concentration (mg/ml). There is an inverse relationship between T1 and phospholipid concentration, and marked shortening of T1 relaxation even at the lower end of phospholipid concentrations tested.

C, T2 relaxivity (1/sec) as a function of phospholipid concentration (mg/ml). T2 relaxivity is linearly dependent on phospholipid concentration (r = 0.99) over the entire range tested (0–250 mg/ml).

D, T2 relaxation (sec) as a function of phospholipid concentration (mg/ml). There is an inverse relationship between T2 and phospholipid concentration.

Note: Error bars are not included, because the size of the dots exceeds the magnitude of the error.

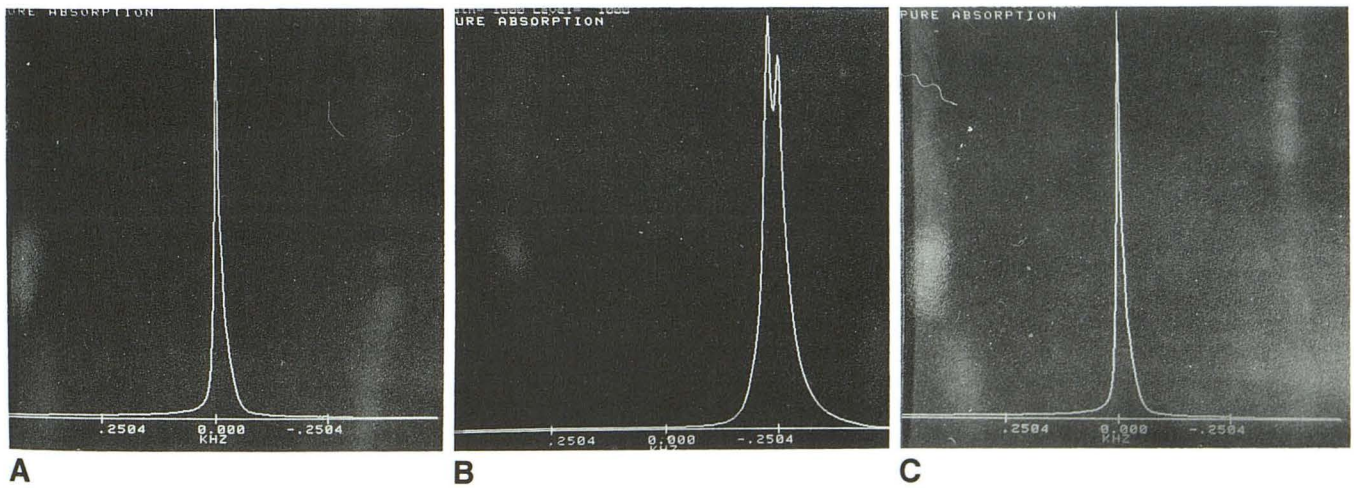

Fig. 2.—*A–C*, Proton spectroscopy at 1.5 T of phosphate buffered saline (*A*), mineral oil (*B*), and phospholipid vesicles in aqueous suspension (*C*). The mineral oil MR signal is shifted 3 ppm relative to the PBS standard, typical of most lipid protons. The phospholipid signal is at the same frequency as the standard, indicating that the signal is *not* from the lipid moiety but from the solvent water proton.

analogous to the neurohypophysis. In contrast, vasopressin has no effect on relaxivity, be it in solution or within liposomes.

The NMR spectra of the liposome suspension, the Mn-PBS, and the mineral oil are shown in Figure 2. Of particular importance is that the liposome solution has a single peak in its NMR spectrum and that peak is not chemically shifted with respect to water. This indicates that the T1 shortening observed in the liposome solution originates with water proton resonances and not from the lipid resonances within the liposomes themselves.

The dilution experiment relaxation measurements combined with spectroscopy yielded one other important conclusion. The linear fit of relaxivity over a broad range of concentrations and the lack of any biexponentiality of the relaxation decay were evidence that the relaxivity of water protons is identical within and outside the vesicles, indicating that the phospholipid membrane of the vesicle is highly transparent to the solvent water protons, with fast exchange across the membrane. Exchange times were estimated by other authors to be about 10 msec [13].

MR Imaging

The T1-weighted (500/20) SE image, the proton density (2000/35) SE image, and the T2-weighted (2000/70) SE image demonstrate the expected pattern of MR signal intensity for water in the Mn-PBS solution (dark on T1-weighted, bright on spin density, and brighter yet on T2-weighted images), and for mineral oil (bright on T1-weighted, bright on spin density, and dark on T2-weighted images) (Fig. 3). The liposome solution has a distinctly different signal pattern. Like mineral oil it is hyperintense relative to the buffer solution on the T1-weighted image, but on proton density and T2-weighted images it is intermediate in intensity between saline and mineral oil (Fig. 3). This pattern is identical to that observed in the posterior lobe of the pituitary gland in that the posterior lobe is considerably brighter than adjacent marrow fat in the clivus (analogous to the mineral oil) on both the spin density and T2-weighted images but is of similar intensity on the T1-weighted images.

The persistence of the hyperintense signal from the liposome vial on the fat suppression image (Fig. 3), and its consistency of spatial position on the decreased bandwidth image compared with the spatially shifted signal of mineral oil (Fig. 3), all confirm that the origin of the hyperintense signal is from water protons. Identical observations have been reported for the chemical shift characteristics (or lack thereof) of the neurohypophysis.

Discussion

We have demonstrated that phospholipid vesicles in aqueous suspension have a concentration-dependent effect on reducing the T1- and T2-relaxation rate of water protons. Furthermore, we have shown that on MR images the signal intensity of phospholipid vesicles in aqueous suspension is analogous to that of the neurohypophysis: hyperintense relative to brain and isointense with fat on T1-weighted SE images, slightly hyperintense to fat on T2-weighted SE images, and not chemically shifted with respect to the water proton resonance. Finally, we have shown that the presence or absence of vasopressin in solution or within the aqueous core of the vesicles does not affect the MR signal even at vasopressin concentrations twice that found in the posterior lobe. These findings may fully explain the biological and physical phenomena observed in the neurohypophysis. To this end it is useful to review the histology and physiology of the neurohypophysis, the physical properties of phospholipids, and the relationship of phospholipids to the neurohypophysis.

Histology and Physiology of the Neurohypophysis

The most remarkable histologic feature of the neurohypophysis is the abundant collection of neurosecretory granules in the axons [14–19]. These granules consist of a dense conglomeration of crystalline hormone-carrier protein complexes enveloped by a phospholipid membrane [14–19]. The ensemble of granule and membrane is usually referred to as the neurosecretory vesicle. These vesicles are 100–160 nm in diameter and form the repository for the hormones of the posterior lobe [14, 15].

The hormones stored in the posterior lobe, vasopressin and oxytocin, comprise nine amino acid peptides that are synthesized in the hypothalamus. In the hypothalamus the hormones are coupled to carrier proteins known as neurophysins to form insoluble crystal aggregates [16]. These aggregates are then enveloped by a phospholipid membrane and transported down the unmyelinated axons within the pituitary stalk and stored in the posterior lobe [14–16, 18]. Under the appropriate stimulus the vesicle membrane fuses with the axonal membrane and by a process of exocytosis the vesicle releases its contents into the capillary bed [15]. The fate of the excess vesicular membrane is uncertain [9, 15, 20–22]. Two theories are that it either migrates in a retrograde fashion up the axon back to the hypothalamus for reuse or is phagocytosed by the pituicytes to form intracellular lipid inclusions. The latter theory is supported by the fact that pituicytes proliferate in states of posterior lobe stimulation and that pituicyte foot processes are intimately applied to both axons and capillaries [20–22]. Furthermore, there is evidence that the lipid inclusions increase in states of posterior lobe stimulation [20–22].

Vasopressin is one of two major hormones stored in the posterior lobe. It has created the most interest in MR imaging because of evidence that in states of vasopressin depletion the high signal intensity of the posterior lobe disappears. The total vasopressin content of the posterior lobe is estimated to be 8 IU (0.02 mg) [23], equivalent to a concentration of 0.1 mg/ml of tissue if the vasopressin is uniformly distributed in the 0.2 ml volume of the posterior lobe. We found that even at twice this concentration vasopressin did not affect the MR signal. Therefore, vasopressin itself is an unlikely cause of

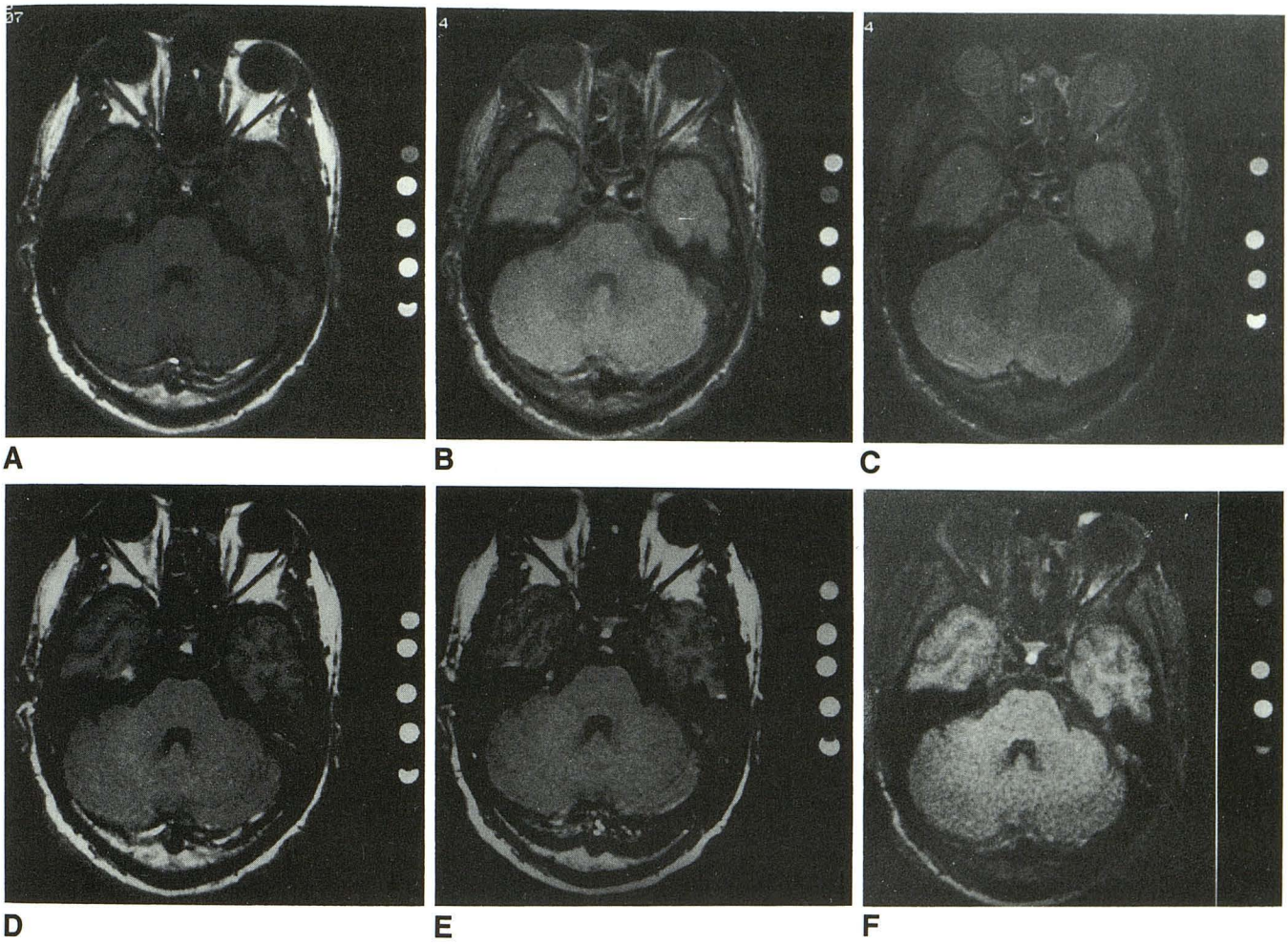

Fig. 3.—Axial MR images of volunteer with phantom. The vials in the phantom are PBS, mineral oil, phospholipid (60 mg/ml), phospholipid (120 mg/ml), and vasopressin in phospholipid vesicles (anterior to posterior).

***A*, T1-weighted (500/20) image. The neurohypophysis, mineral oil, both phospholipid vials, and vasopressin in the vesicles are all bright compared with brain and PBS standard. The meniscus in the vasopressin vial is caused by incomplete filling of the vial. The brain is photographed darker than usual—this has been done on purpose to highlight contrast between the vials, which would otherwise be uniformly bright.**

***B* and *C*, Proton-density-weighted (2000/35) image (*B*) and T2-weighted (2000/70) image (*C*). On a relative scale, the mineral oil is now darker; both phospholipid vials and the vasopressin in phospholipid vesicles maintain high signal, as does the posterior lobe. PBS becomes progressively brighter (relatively) with more T2-weighting.**

***D*, T1-weighted decreased bandwidth image (500/30, bandwidth = ±6 kHz). Frequency encoding is anterior to posterior with fat shifted upfield. Mineral oil shifts upfield; all other vials maintain position.**

***E*, T1-weighted decreased bandwidth image (500/30, bandwidth = ±6 kHz). Frequency encoding is anterior to posterior with fat shifted downfield. Mineral oil shifts downfield; all other vials maintain position.**

***F*, Fat suppression image (hybrid method, see "Methods" for details). Head and phantom images were acquired separately so that both could be at isocenter during imaging. This technique is subject to significant degradation for off-center objects due to field nonuniformities.**

Note that the mineral oil signal disappears; all others are maintained. Parts *D–F* confirm that the phospholipid signal is not from the lipid moiety but from solvent water protons.

the signal of the neurohypophysis. This is in keeping with previous experiments that have shown that small proteins like albumin are unlikely to be significant relaxation enhancers, even at high concentrations [24, 25]. We did not investigate the possibility that the crystalline aggregate (vasopressin-neurophysin) may affect MR relaxation but we feel that this is unlikely as the crystals are insoluble and therefore effectively segregated from the aqueous compartment, except for possible surface interactions.

There are two models of vasopressin depletion that have been examined with MR: diabetes insipidus in humans and prolonged administration of hypertonic saline to animals. In both cases the normal high signal intensity of the posterior lobe seen on MR is absent [1, 6, 9, 10]. In diabetes insipidus the posterior lobe is depleted of vasopressin; histologically, the tissue is degranulated and devoid of vesicles, and the axons are degenerated with the hypothalamic nuclei depopulated of cells. The fate of pituicytes and their lipid inclusions

in diabetes insipidus is unknown. In prolonged administration of hypertonic saline to rabbits, similar histologic features have been demonstrated and correlated with the disappearance of the high intensity from the posterior lobe, the only difference being that the axons do not degenerate. In the rabbit model, lipid inclusions were not found in pituicytes, but they are well-recognized in other mammalian species, including humans [6, 15, 26].

The Neurohypophysis and Phospholipids

Phospholipids, usually in combination with cholesterol, are components of all biological membranes and are found throughout the body. Phosphotidylcholine is the major, but not the only, phospholipid in the pituitary gland. Other lipids found in the posterior lobe include cholesterol, cholesterol esters, sphingomyelin, triglycerides, and fatty acids (Paradis and Kates, personal communication). In the neurohypophysis, phospholipids are found in the axonal membranes, the membranes surrounding each of the neurosecretory granules, and within pituicytes. The total phospholipid and cholesterol concentration in the neurohypophysis is high, (25 mg phospholipid and 15 mg cholesterol per ml of tissue) approximately 30–40% higher than that of the adenohypophysis (Paradis and Kates, pers. com.). The differential lipid content between the two lobes could explain the higher signal intensity of the posterior lobe compared with the anterior lobe.

MR Characteristics of Phospholipids and Phospholipid Vesicles

Typical triglycerides consist of a glycerol backbone connected to three fatty acids by ester linkages. They are hydrophobic and insoluble in water. Phospholipids differ from triglycerides in that one fatty acid is replaced by a polar head group; in phosphotidylcholine the head group is choline. The polar head group results in hydrophobic and hydrophilic ends in the phospholipid molecule. Typically, in biological membranes the hydrophobic groups face each other in the interior of the membrane and the hydrophilic groups face outward toward the aqueous phase. The phospholipid vesicles used in this experiment have a similar structure.

Phospholipids have a large number of hydrogen nuclei within the molecule, mostly within the fatty acid groups. However, these lipid protons have a very short T2 owing to restricted mobility and therefore do not contribute to the MR signal [27]. Some authors [6] have assumed that phospholipids therefore cannot affect the MR signal; others [28, 29] have noted T1 shortening at high concentrations of phospholipid but have falsely attributed this to the lipid moiety, not to the effect of phospholipid on the aqueous phase. We have shown that the lipid protons are invisible under normal MR conditions but that the phospholipid membranes exert a significant relaxation effect by enhancing the T1 relaxation of water protons. The mechanism is probably by a dipolar cross-relaxation between the polar end of the lipid bilayer and an aqueous layer adjacent to it [30–33]. The lipid membrane acts as a relaxation sink by providing restricted rotational stability for the bound water layer. The bound water exchanges rapidly with the free solvent water. However, our own current work has demonstrated that the enhanced relaxation is not mediated by spin transfer for either liposomal solutions or the posterior pituitary gland as is the case in myelin [32, 33]. No diminution of signal is evident in saturation transfer experiments.

The relaxation effects of membrane lipids are powerful. Membrane lipids may have a tenfold greater interaction with water per unit interface than an analogous protein-water interfacial interaction [33]. Our data, when compared with studies of albumin solutions [24, 25] supports the view that membrane lipids are more powerful relaxation enhancers than are small proteins.

An Explanation for the Appearance of the Neurohypophysis?

Our results are entirely consistent with the literature. We propose the following hypothesis to unify the findings of previous reports on this subject.

The hyperintense signal of the neurohypophysis originates with water protons that have enhanced relaxivity induced by tissue phospholipid membranes. These phospholipids are present in the axonal membrane, the neurosecretory vesicular membrane, and in pituicytes. The distribution of phospholipids between these compartments is not known, but, histologically, axonal endings and neurosecretory vesicles are more numerous than pituicytes and therefore likely to contain the majority of the posterior lobe phospholipids.

We have shown that the higher the phospholipid concentration the greater the signal on T1-weighted images. Thus, it would be expected that the posterior lobe with its accumulation of neurosecretory vesicles in addition to axons and pituicytes would be brighter than the pituitary stalk. In disease states in which axons, vesicles, or pituicytes diminish in number, phospholipid concentration would decrease and the gland would be less intense. In cases of stalk transection, the distal segment undergoes axonal degeneration and is depopulated of vesicles. As expected, the signal disappears [34–36]. In diabetes insipidus, axons degenerate and vesicles dissipate; in animals fed hypertonic saline, vesicles also disappear—in both cases the signal normally seen in the posterior lobe is absent [1, 6, 10]. Thus, the argument that vasopressin and/or its neurophysin *must be responsible* for the signal is *not* valid, since, in large part, phospholipids and the hormone are found together in the same particle. To date there has been no model in which the MR signal of the neurosecretory granule could be separately analyzed from that of the surrounding vesicular membrane. On these grounds, either could be invoked as the source of the posterior lobe signal. However, we have shown that phospholipids can account for MR properties similar to that of the posterior lobe and that vasopressin cannot. This does not prove that phospholipids are exclusive in this effect, but they are the only material analyzed to date that are associated with the neurosecretory process and that have the proper MR char-

acteristics to explain in vivo observations. It is likely that the lipid inclusions in pituicytes [9] are a minor contributor to the total relaxation enhancement when compared with the effect of phospholipids in vesicle and axonal membranes.

In the white matter of the adult mammalian brain the concentration of phospholipids has been estimated to be about 75 mg/g wet weight [37]. Phospholipids in white matter are likely to cause significant T1 shortening [32, 33], but a direct analogy cannot be made to the neurohypophysis because the access of the water proton to the lipid membrane is more restricted in myelinated white matter than it is in the unmyelinated posterior lobe. Equal amounts of phospholipid could therefore have substantially different effects on relaxation in the two tissues.

Clearly, our study with pure phosphotidylcholine vesicles is an overly simple model of real biological membranes, which are much more complex and usually contain cholesterol, proteins, and other materials. Any of these could potentially augment cross-relaxation by either altering the correlation time of the bilayer or increasing the number of water molecules available for this process [33]. Indeed, by our calculations the amount of phospholipid in the posterior lobe is about one half that required to fully account for the short T1 relaxation of the posterior lobe if phospholipids were the only lipids capable of enhancing the relaxivity of water. However, other factors need to be considered, including the facts that there are other lipids present that could act in a similar manner and that the relatively high cholesterol content could further augment T1 relaxivity [31]. However, the phospholipids in themselves are an excellent approximation for the MR characteristics of the posterior lobe and they illustrate the importance of large immobilized arrays of macromolecules as relaxation enhancers.

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The reader's attention is directed to the commentary on this article, which appears on the following pages.