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**Hyperintense signal on MR images of the
pituitary gland.**

I Fujisawa

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believe that the presence of an ectopic neurohypophysis always indicates an injury to the hypothalamoneurohypophyseal tract, although that injury may be temporally remote.

The two cases illustrated in the paper by Benshoff and Katz have imaging characteristics much more in keeping with lipomas than with ectopic neurohypophyses.

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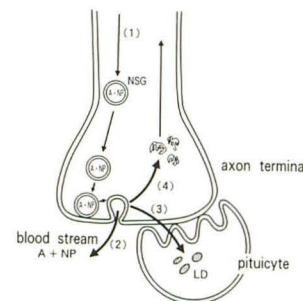
Hyperintense Signal on MR Images of the Pituitary Gland

The source of the hyperintense signal in the posterior lobe of the pituitary gland on T1-weighted MR images is controversial. In 1987, my colleagues and I [1] hypothesized that the signal reflects the functional integrity of the hypothalamoneurohypophyseal system and that the probable source of the signal is neurosecretory granules. Subsequently, Kucharczyk's group [2] proposed the hypothesis that lipid droplets within the pituicytes are the source of the hyperintense signal. In 1988, they reported an experimental study [3] and concluded that the lipid droplet theory or the neurosecretory granule theory was correct. In the paper "The Effect of Phospholipid Vesicles on the NMR Relaxation of Water: An Explanation for the MR Appearance of the Neurohypophysis?" [4] in the July/August 1990 issue of the *AJNR*, they proposed a newer hypothesis: the phospholipid theory. The phospholipid theory states that the high concentration of the total phospholipid in the posterior lobe, existing mainly in the lipid droplets within the pituicytes and in the membranes of the axons and the neurosecretory granules, is the source of the hyperintense signal. I read their paper with great interest and found some problems.

In their discussion (p. 697 in [4]), they describe what they had done and mention the saline overload experiment in their 1988 paper [3]. In fact they did not do this experiment. In 1989, my colleagues and I [5] reported an experimental study that showed that the hyperintense signal in the posterior lobe disappeared after 2 weeks of administration of hypertonic saline solution, which stimulated the release of antidiuretic hormone from the posterior lobe. In their 1988 experiment, Kucharczyk et al. observed that the hyperintense signal increased in volume under the stimulation of release of antidiuretic hormone. The results of the two experiments were quite opposite. Which result is correct is the key to solving the controversy.

Previously, my colleagues and I [6] indicated several serious problems in the 1988 experiment. Here, I point out an additional one, which contradicts the phenomenon Kucharczyk et al. observed in the posterior lobe. An understanding of the mechanism of hormone release at the axon terminal is necessary for evaluation of their 1988 and 1990 experiments and our 1989 experiments.

Fig. 1.—Diagram of axon terminal. Neurosecretory granules (NSGs) containing antidiuretic hormone (A)—neurophysin (NP) complex are transported to axon terminal in posterior lobe (1). At axon terminal, contents of NSGs are released into blood-stream by exocytosis when A and NP separate (2). Membranes of NSGs become excessive when release of A is stimulated. Two hypotheses about the fate of the excessive membrane have been proposed: It is phagocytosed by pituicytes to form lipid droplets (LD) (3), or it migrates up the axon to the hypothalamus for reuse (4). Phospholipid exists in LDs within pituicytes and in membranes of NSGs, axons, and pituicytes. When function of posterior lobe is stimulated, the number of NSGs in posterior lobe decreases, but excessive membranes of NSGs and total phospholipid increase.



Glial cells in the posterior lobe are called pituicytes. Historically, it was known that lipid droplets exist within the pituicytes, especially in the rat [7]. At first, researchers thought that the pituicytes were glandular cells and that the lipid droplets were secretory granules. Those ideas were disproved by two new findings. One was the neurosecretory theory. The other was that two of the posterior lobe hormones, antidiuretic hormone and oxytocin, were found to be oligopeptides and not lipids. Some researchers [8, 9] concluded that the pituicytes were not related to the function of the posterior lobe. Still others [10, 11] proposed that excessive membranes of the neurosecretory granules at exocytosis are the source of the lipid droplets in the pituicytes (Fig. 1). They observed that the number of droplets increased when the function of the posterior lobe was stimulated. The number of neurosecretory granules decreased under such conditions. In their 1988 paper, Kucharczyk et al. [3] reported that they had observed a significant increase of both lipid droplets and neurosecretory granules in dehydration-stimulated animals. The neurosecretory granules should decrease under such conditions. Concerning the fate of the excessive membranes of the granules, another hypothesis is that the granules migrate in the axon up to the hypothalamus for reuse [12] (Fig. 1). Synthesis and release of antidiuretic hormone is thought to increase the excessive membranes at the axon terminals and consequently to increase the total amount of phospholipid in the posterior lobe because the membranes contain phospholipid. Thus, both the lipid droplet and the phospholipid theories do not explain the absence of the hyperintense signal observed in the posterior lobe in the hypertonic saline overload experiment.

In their results, Kucharczyk et al. [4] concluded that the pattern of signal intensities of liposome solutions was similar to that of the human posterior lobe. However, I believe that the liposome solutions had signal intensities markedly higher than those of the posterior lobes of volunteer subjects on proton-density and T2-weighted MR images (Figs. 3B and 3C in [4]). I think that it is incorrect to equate the liposome solutions and the human posterior lobe model. The significance of the 1990 experiment [4] is that the liposome, the size of which is similar to that of the neurosecretory granule in the posterior lobe, induced a remarkable shortening of relaxation times. I think that the mechanism observed in the 1990 experiment may explain the neurosecretory granule theory.

In 1987, my colleagues and I [13] first reported the ectopic posterior lobe in patients with pituitary dwarfism and hypothesized that the ectopic lobe is caused by stalk transection at birth because of the high correlation with abnormal delivery. In 1988, Kucharczyk's

group [14] proposed the new idea that the ectopic posterior lobe is a maldevelopment of the posterior lobe. Currently, in pediatric endocrinology, the cause of the ectopic posterior lobe in dwarfism is still controversial [15]. In the discussion (p. 698 in [4]), Kucharczyk et al. referred to their 1988 paper as the stalk transection report. I would like to know why they have abandoned their maldevelopment theory.

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Reply

I am pleased to have the opportunity to respond to Dr. Fujisawa's letter about our recent publication on phospholipid vesicles [1]. He has summarized his views on the hyperintense signal found in the posterior lobe of the pituitary gland on T1-weighted MR images, and he has chronicled his and his colleagues' publications on this subject [2-6] as well as those of which I am a coauthor [1, 7-9]. Dr. Fujisawa has accredited the papers that I participated in as being from "Kucharczyk's group." As a point of clarification, although I would like to, I cannot count the many authors and coauthors of these publications as being "my group." Our collaboration has not extended to all

the papers Dr. Fujisawa refers to, nor do we really function as a group. Because I cannot represent all the views of those individuals, I have chosen to respond personally rather than for the group.

Dr. Fujisawa and his colleagues have several important papers [2-6] on the subject of the posterior lobe. They have localized the hyperintense signal to the posterior lobe, documented aberrations of the signal in certain states (diabetes insipidus and pituitary dwarfism, in particular), and shown the lack of chemical shift in the signal. I agree fully with these findings and have never stated or published anything to the contrary. The only significant point of disagreement between us is the cause of the hyperintense signal.

Dr. Fujisawa and I have pursued different avenues in our attempts to answer this puzzle. I think that we both agree that the hyperintense signal is unique to the posterior lobe and is somehow related to the secretory integrity of that structure. I think that because of the association between the signal and the secretory function of the posterior lobe, Dr. Fujisawa has directed his efforts to proving that the signal emanates from vasopressin or a closely associated protein, neurophysin. This is an attractive hypothesis and one that I and others have considered, and still consider possible. If proved, it would be a simple and straightforward explanation for the hyperintense signal.

Dr. Fujisawa's work has been focused on showing the association between the presence or absence of neurosecretory material in the posterior lobe and the presence or absence of the hyperintense signal. He has shown this association elegantly in a rabbit model [6]. To the best of my knowledge, however, he has not actually shown, nor has he proposed, a plausible mechanism by which the neurosecretory material of the posterior lobe can cause short T1 relaxation. In experiments with a concentrated solution of vasopressin, my colleagues and I [1] failed to show any significant T1 shortening with this protein. I also am unaware of anything in the literature that has shown this effect with vasopressin or other small peptides.

I, on the other hand, have chosen to pursue a different approach to this problem. As I have already stated, assigning the hyperintense signal to the neurosecretory material is a highly attractive hypothesis but one that is difficult to support because small proteins do not cause significant T1 shortening at the concentrations found in the posterior lobe [1, 10]. Because of the difficulty in finding a mechanism for, or proof of, T1 shortening with vasopressin or other small proteins, I chose to examine materials that could be shown to have a short T1 or to cause T1 shortening, determine whether they exist in sufficient quantities in the posterior lobe to account for the hyperintense signal, and then evaluate whether an increase or decrease of the material in the lobe could be provoked and correlated with a change in the signal.

Review of the literature with respect to the contents of the posterior lobe revealed few candidate materials with the potential to fulfill these criteria except the curious lipid inclusions in pituicytes. Therefore, lipid inclusions were the first material examined [8]. My colleagues and I found that the lipid inclusions and the hyperintense signal increased in parallel in cats dehydrated for 48 hr [8]. Shortly thereafter, Fujisawa et al. [6] published the statement that "the lipid droplets in the pituicytes consist of phospholipids, which have no visible signal in proton MR imaging." We were performing relaxation experiments with phospholipid vesicles at the time that article was published. Contrary to what Fujisawa et al. stated, we found that phospholipids did shorten T1 [1]. I do not consider experimentation with phospholipids a new hypothesis, as Dr. Fujisawa claims, but a logical extension of our earlier work. However, the phospholipid experiments have produced interesting results that may have wider application in MR beyond that of the pituitary gland, regardless of what the hyperintense signal is. It is ironic that having stated that phospholipids do not affect the MR signal, Dr. Fujisawa now thinks

that "the mechanism observed in the 1990 [Kucharczyk et al.] experiment may explain the [Fujisawa et al.] neurosecretory granule theory." This statement is purely speculative; Dr. Fujisawa has no experimental data to support his hypothesis. It is also unclear to me whether Dr. Fujisawa now concedes that phospholipids can increase T1 relaxivity.

I think that we all have a rather narrow focus on what various tissues and materials can or cannot do to the MR signal, and we, myself included, should refrain from making blanket statements on topics we have little experience with. With that in mind, I have continued to consider the possibility that neurosecretory granules may enhance T1 relaxivity but through a mechanism we only recently have considered. Currently, I am unsure whether T1 effects with neurosecretory granules can be demonstrated. I do not yet have a good model for the granule, but recent work [11] with calcium has shown substantial signal hyperintensity through T1 shortening effects due to a mechanism of water adherence to the crystal surface. The rotational and translational motion of the surface water is reduced by the crystal surface, making conditions for efficient T1 relaxation more favorable. It will be interesting to determine if small crystalline protein aggregates like the neurosecretory granules have the same effect. If so, it would be an important step in proving the neurosecretory granule hypothesis.

Finally, to address Dr. Fujisawa's specific criticisms, I suggest that many of his comments are incorrect and others are trivial. He states that my colleagues and I claim to have done a saline overload experiment. I closely reread the papers [1, 7-9]; we made no such claim. The reference citation that seems to trouble him actually was referring to diabetes insipidus in humans [7]; he misinterpreted the citation. He also believes the phospholipid vesicles "had signal intensity markedly higher" than the posterior lobe. I, and apparently the *AJNR* reviewers of our manuscript, thought the two signals were quite similar. In reference to posterior lobe ectopia in dwarfism, Dr. Fujisawa would like to know why "they have abandoned their maldevelopment theory." I still think, as I did then, that whatever is responsible for the hyperintense signal, it accumulates above the atretic or transected distal pituitary stalk. The term maldevelopment is Dr. Fujisawa's, not mine. In 1988, I thought the hyperintense nodule in pituitary dwarfs most likely was a lipid, but if neurosecretory granules can be shown to cause the hyperintense signal, I would accept the neurosecretory granule theory.

Dr. Fujisawa's diagram (and accompanying explanation) is his most relevant criticism, and it raises an important point. He and his colleagues have shown experimentally that the hyperintense signal disappears after 2 weeks of saline overload [6], and he suggests that phospholipids would accumulate, not diminish, under these conditions. His argument makes sense if we accept the premise that all the phospholipids that are liberated at the terminal axon are taken up and accumulate in the pituicytes and that the pituicytes do not metabolize the phospholipids. But we do not know this. We have some experimental evidence that after 48 hr of dehydration, the lipid inclusions increase [8], but we do not know what happens after 2 weeks of dehydration. Does Dr. Fujisawa have data to indicate an accumulation of phospholipid in the pituicyte after 2 weeks of dehydration? I currently do not have any data of my own to support or refute this claim.

In conclusion, the hyperintense signal has provided a stimulus to examine T1 relaxivity of various tissues. I have learned a great deal from all the experiments that have been performed. We should continue the learning process and perform the experiments required to solve the remaining pieces in the posterior pituitary puzzle.

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Editor's note.—See related article by Mark et al. on pages 529-532 in this issue.

CT Diagnostic Features of Choroidal/Hippocampal Fissure Complex in Alzheimer Disease and Progressive Supranuclear Palsy

We read with interest the paper by George et al. [1] about the presence of a characteristic hippocampal lucency on CT scans of patients who have Alzheimer disease. Some years ago, we reported the same finding on the CT scans of patients who have progressive supranuclear palsy [2, 3].

Degenerative changes in the hippocampal cortex, especially in the Sommer sector, have been reported in progressive supranuclear palsy [4, 5]. They consist of neurofibrillary tangles in the cerebral cortex and, in the opinion of Ishino and Otsuki [5], are a specific manifestation of this disease and are not age-related.

We think that these bilateral hippocampal lucencies, associated with the other well-known CT findings characteristic of progressive supranuclear palsy [6], could be an important feature in the diagnosis of the disease.

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