

THE RADIOISOTOPIC ASSESSMENT OF CEREBRAL EDEMA

by

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Our ability to demonstrate the regional deposition of radionuclides within the brain has provided a useful clinical tool. Traditional brain scanning, however, is limited to detecting a gross breakdown in "blood brain barrier". There are, however, many brain abnormalities which are not identified by this rather gross technique. More subtle regional alterations may be detected if we could estimate the transport of a selected substance from the intra- to extravascular space within the brain. With this goal in mind, we have used a multi-label approach to demonstrate the intra- and extravascular space in experimental forms of brain edema. Our ability to discern cerebral edema and to differentiate the type of edema (i.e. primarily osmotic or related to gross endothelial damage) should afford an increased fidelity in recognizing focal cerebral dysfunction and may be useful to guide therapy once the pathophysiologic mechanism are more clearly understood.

Previous investigators have defined the various brain spaces for labelled radionuclides. Labelled red cells have been used to identify the red cell content of the brain as a reference marker for brain vascular volume. I-131 labelled antipyrine has been used to define the brain water space, which is relatively constant in many pathologic states thus far investigated. We have used the constant brain water space in relationship to brain red cell mass to indicate the changes in regional brain blood volume per unit brain mass. In addition, we have studied the brain albumin space in relationship to vascular volume and brain mass as an index of increased endothelial leak in pathologic situations. Using a reference label for brain mass (labelled antipyrine), for vascular volume (labelled RBC) and a label of transcapillary protein exchange (labeled albumin) we have distinguished water induced brain edema from tin induced edema in the

experimental animal.

METHODS

In white female NLR strain rats weighing 100-125 grams, 20-25 ml intra-peritoneal sterile, pyrogen free water was used to induce water edema.¹ Tin edema was induced² by injecting a sterile solution of triethylen-tin bromide into peritoneal cavity (7mg/kg). The five minute brain RBC and albumin spaces were determined with ⁵⁹Fe-tagged donor RBC's and ¹³¹I-human serum albumin. Control groups were compared with two experimental groups, i.e. three hours after the water injection and 24 hours after the tin injection. At least six animals were studied in each group and the results depicted as percent of the control space for each group.

This single injection (five minute antipyrine space) resembles the equilibrium value as checked by comparing groups at 1 minute, 5 minutes, 15 minutes and 30 minutes post single IV injection with groups undergoing constant infusion to equilibration (Figure 1).

Also, antipyrine and technetium spaces were studied in controls and water edema groups at 1 minute, 5 minutes and 15 minutes post IV injection using ¹²⁵I-antipyrine and Na ^{99m}TcO₄.

Femoral venous blood (0.5ml) was removed immediately prior to sacrificing the animal in liquid nitrogen. The venous blood samples were subsequently used to estimate systemic intravascular (whole blood) radioactivity and systemic plasma radioactivity. Whole (frozen) brains were removed and placed into pre-weighed counting vials. All samples were counted against standards, using pulse height analysis to separate the various radionuclide labels. The antipyrine space correlated with the brain water content by measuring weight loss after drying (80°C for 72 hours) to a constant weight.

The brain RBC space, antipyrine space, albumin space and technetium space were calculated by using the following formulas:

$$\text{Total RBC space in brain} = \frac{\text{brain } ^{59}\text{Fe cpm}}{1 \text{ ml blood RBC} - ^{59}\text{Fe cpm}}$$

$$\text{Total albumin space} = \frac{\text{brain } ^{125}\text{I-HSA cpm}}{1 \text{ ml plasma } ^{125}\text{I-HSA cpm}}$$

$$\text{Total antipyrine space} = \frac{\text{brain } ^{131}\text{I-antipyrine cpm}}{1 \text{ ml plasma } ^{131}\text{I-antipyrine cpm}}$$

$$\text{Total } ^{99\text{m}}\text{Tc space} = \frac{\text{brain } ^{99\text{m}}\text{Tc cpm}}{1 \text{ ml plasma } ^{99\text{m}}\text{Tc cpm}}$$

RESULTS - DISCUSSION

The 1 minute antipyrine space equaled 100%, 94% of the brain water in the control and experimental groups respectively, tending to confirm the use of this measurement as a reference index of brain mass for purposes of estimating vascular volume change in brain edema. The simplified 5 minute antipyrine space was also compared with the more rigorous equilibrium value (Figure 1).

Water induced brain swelling was characterized by a marked decrease in brain RBC mass and albumin space with a slight (albeit non-significant) increase in the brain antipyrine space and water content (Table 1). Thus, the simultaneous estimation of these spaces can reliably discern a change which is not revealed with $^{99\text{m}}\text{TcO}_4$. Time dependent observations suggest that the five minute space is as useful as any to demonstrate these changes (Figure 2).

The albumin space in tin induced brain edema was strikingly different from that seen in water intoxication consistent with the electron microscopic data suggesting a endothelial defect in tin edema. In the tin

treated animals the red cell space was markedly decreased while the albumin space was markedly increased from the normal (Figure 3). The five minute albumin/RBC space ratio increased to 118% of the control value while in water intoxication this ratio resembled the control value.

Oldendorf has demonstrated the feasibility of pulse height analysis to distinguish intracerebral from extracerebral radioactivity³. This is ideally suited for such isotopes as Indium 113m with its characteristics radiation of 24-28 kv and its maximum or major rate energy at 390 kev. By using a ratio of the major energy to characteristic energy, one can discern that portion of radionuclide located within the brain versus that portion located outside of the cranial vault. ^{113m}In has been used as a plasma protein label to estimate plasma volume⁴. Similarly, it is also possible to distinguish the intracerebral from extracerebral antipyrine (using ¹³¹I and ¹²⁵I). It, therefore, is feasible to develop dual isotope (or single isotope techniques at dual energy ranges) to detect intracerebral from extracerebral antipyrine and plasma protein in a clinical setting. Although it is possible to detect brain red cell content by similar techniques, these studies suggest that quantitative information of brain plasma protein space per unit brain mass (obtained by using the antipyrine space as an index of brain water) may provide useful clinical information. It seems reasonable that these techniques may improve our ability to recognize early edema in pathologic states where the brain scan is now normal. Examples of where this may be useful include early acute stroke and in some cases of head injury, which are characterized by edema and a normal brain scan. This dual isotope approach may more clearly demonstrate altered protein transport in relationship to regional brain mass than any previous method.

These results suggest further studies to investigate whether the

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recognition of a pathophysiologic edema mechanism has therapeutic implications. Edema induced from water intoxication, characterized by a low red cell mass in relationship to water space can perhaps best be managed by osmotic diuresis whereas edema characterized by a damaged endothelium and increased extravascular plasma protein may be more responsive to the endothelial effect of steroid. Admittedly, clinical states may represent a mixture of these two discrete mechanisms. Further studies to document the efficacy of these various therapeutic modalities as indicated by these diagnostic techniques are in progress.

These studies confirm the tracer capability of recognizing more subtle forms of brain edema than is now possible with the standard brain scanning agents, i.e. $^{99m}\text{TcO}_4$ did not demonstrate a significant difference between the abnormal and normal structures.

Thus, we have been able to distinguish water from tin induced brain edema in the experimental animal by their remarkable difference in alteration of brain tracer space. In tin edema the endothelial damage results in increased protein transport across the endothelial wall causing an increased brain albumin space in relationship to brain red cell mass. Water induced edema on the other hand does not increase the brain albumin space, but rather decreases the brain blood volume in relationship to the brain water space. The ability to discern these variations in brain transport process may provide the basis for clinically useful techniques which improve the diagnostic accuracy of brain scanning.

SUMMARY

The brain antipyrine, red cell albumin and technetium spaces have been studied in the experimental animal. Control animals were compared with brain edema induced either by water intoxication or triethyl tin. The water intoxication is characterized by a decrease in the red cell

space and an increase in albumin space. These observations and the ability to develop techniques with multiple isotopes suggest that it may be possible to clinically recognize and differentiate more subtle forms of brain swelling than is now possible with conventional brain scanning.

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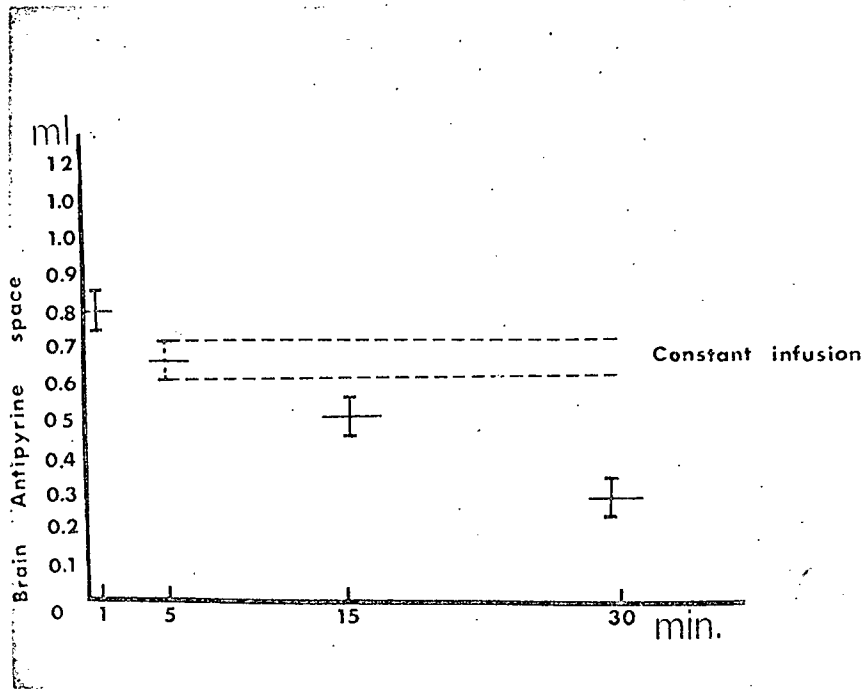


FIGURE 1

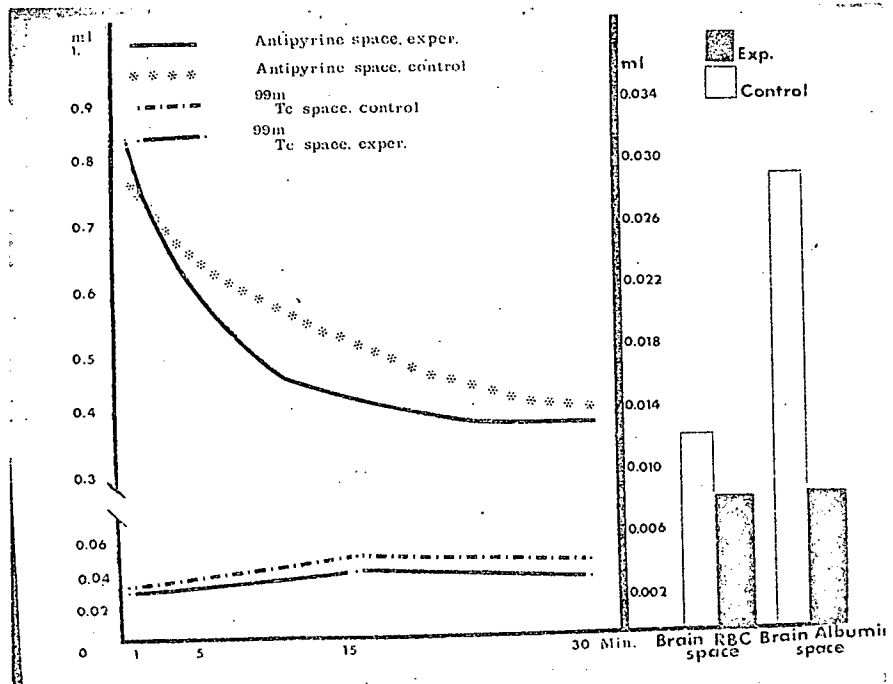


FIGURE 2

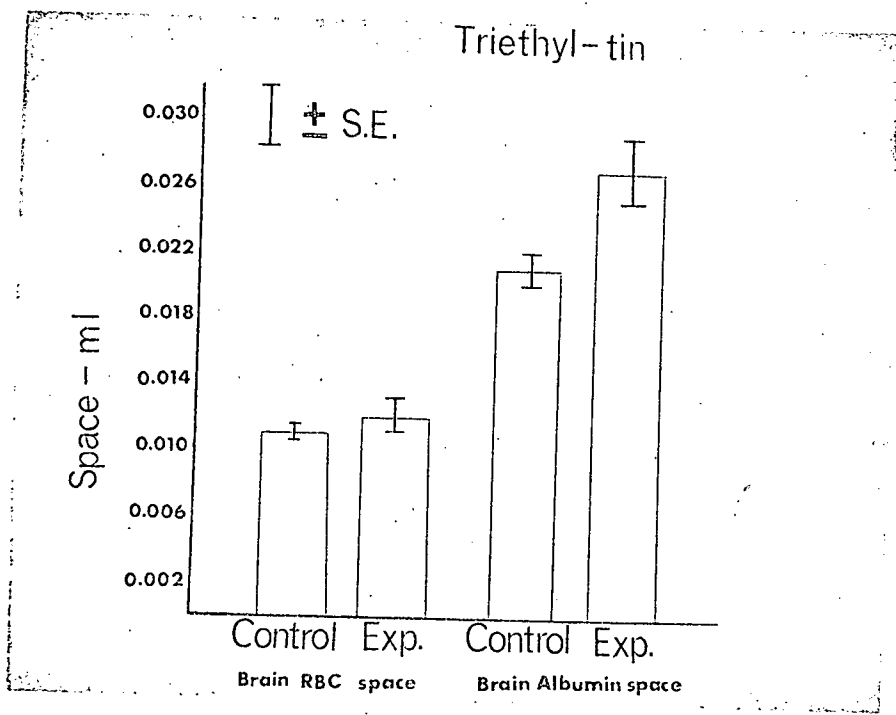


FIGURE 3