Cerebral Ammonia Metabolism

To the Editor:

I have read the paper by Phelps, Hoffman, and Raybaud "Factors Which Affect Cerebral Uptake and Retention of NH3" (Stroke 8: 694, 1977) with considerable interest, because of my own concern with cerebral ammonia metabolism. There are several questions that I would like to ask concerning their paper. What was the concentration of the ammonia in the test bolus? If it was 10^-4 moles per ml, the ammonia concentration would be 100 times greater than the highest concentrations usually associated with the most severe cases of hyperammonemia. The method used to make this measurement was not specified. The authors cited earlier reports by Raichle et al. (Am J Physiol 230(2): 543, 1976) in order to validate their methods. The validity of the authors' data depends on complete mixing of the test bolus with the blood flowing through the internal carotid artery before it reaches the cerebral capillary bed. Furthermore, the addition of the test bolus must not alter the concentration of ammonia or the pH of the blood as they mix. The study of Raichle et al. did not require these assumptions. The authors have not discussed this in their paper.

The similarity of the time course for the passage of the test bolus through the brain to that reported by Oldendorf (Brain Res 24: 372, 1970), where complete clearing of the blood from the cerebral vessels has been observed, suggests that, in fact, little mixing occurred. Although the literature concerning the effect of pH on ammonia extraction is conflicting, earlier studies by Carter et al. (Neurology 23: 204, 1973), who did their work at the same institution as the authors, as well as more recent unpublished studies by my colleagues and me, have shown major effects on brain ammonia uptake after changes in pH. Their negative finding is easily explained by a lack of mixing of the test bolus. This effect could also produce erroneous results concerning the effect of different ammonia concentrations.

Finally, in the discussion, the authors speak of an ammonia turnover rate of 75% per second. The reference they cite is a textbook. Consultation of the primary reference cited in the text indicates that the data from which that calculation was made were the result of applying methods that were not consistent from observation to observation, and are no longer believed to be valid in studies of labile brain metabolites.

For the reasons that I have mentioned, I have considerable doubt about the validity of their study, especially the data that were obtained after intracarotid 13-N-ammonia injections.

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The authors reply:

The questions raised and comments made by Dr. Lockwood reflect his detailed review of the work we presented and I would like to address each of Dr. Lockwood's points individually.

The carrier ammonia concentration was not 10^-4 moles/ml. It was measured to be less than 10^-3 Molar (M) as stated in our paper and as determined by Straßmann and Welch.1 No mass peak was detected with chromatographic analysis which had a lower limit of detection of 10^-4 M. Since the 10^-3 M is close to the normal circulating levels of ammonia in this work, the actual value is less than 10^-4 and we found no effects on single pass 13NH3 retention. After increased circulating ammonia concentration up to about 10^-3 M, this point of concern should be removed.

The concern over mixing is one which all of the people using this method at Washington University and myself have extensively investigated. However, due to the fact that we have published this method as a part of different studies, it was not extensively described in our STROKE paper. 1 Where the mixing is less important in the paper cited as a reference2 it is critical for the measure of oxygen metabolism for which this method was developed. 3 4 In the 13NH3 work reported in STROKE there was a key point in the method which should have been reitered. In all the studies the 13NH3 was added to a blood sample (arterial blood from the carotid catheter) withdrawn from the animal in the state under study. This was done to eliminate concern over mixing and distribution of pH, ammonia, O2, CO2, glucose etc. concentrations in local environment of the capillaries where extraction is taking place.

The point made by Lockwood, that some "similarity" exists between the shape of the 13NH3 residue curve (fig. 1) and the "curve" in figure 1 of Oldendorf's paper,4 to imply that mixing was a problem in our studies, is a bit confusing to me. Oldendorf's studies were purposely carried out in such a manner that the injected solution did not mix with blood at all as opposed to our studies where we are examining the extraction of 13NH3 from the circulating blood. Oldendorf only shows a couple of data points, not a curve. However, in any case, it is not obvious to me how this sheds any light on any potential mixing problem in our studies. Figure 1 clearly shows how our residue curve can be analyzed into 3 compartments as stated in the paper: i) an extracted portion that has a large-volume of distribution and long retention time in that volume (e.g., distributed through extracellular space and metabolized to amino acids), ii) a rapidly clearing portion which exhibits a volume of distribution and mean transit time equal to a vascular component at the measured CBF, iii) a third and very small (~1 to 3%) component due to recirculation of the tracer. In fact, although not reported, studies were carried out at a constant CBF level in which 13NH3 was injected into the intracarotid artery to obtain the single pass extraction curve, 213NH3 was injected intravenously to measure recirculation and 3CO2-red blood cells were injected into the intracarotid artery to measure the vascular clearance curve and calculate the vascular mean transit time. These studies were actually carried out and rigorously analyzed to see if we could detect any back diffusion of 13NH3 from the extracellular space. From this data we clearly fit the shape of the curve by the 3 components given above and there was no apparent back diffusion (e.g., 13NH3 was unidirectionally transported and apparently metabolically trapped in the tissue). Thus, I think the explanation we gave in our paper for the shape of the 13NH3 residue curve is valid and I don't think Oldendorf's data suggest anything about our data.

The question of pH dependence is more difficult. We should keep in mind that the STROKE paper dealt with a single pass extraction that appears to be unidirectional. This condition is obviously different from steady state conditions (e.g., in the normal basal state the net extraction of circulating ammonia by the brain is close to zero while the single pass extraction of 13NH3 is about 40%). In the paper by Carter et al.,5 it is difficult to draw detailed conclusions because the animals' respiration was not controlled, and PaCO2 and, therefore, cerebral blood flow (CBF) was allowed to vary. In fact, the average PaCO2 at their elevated pH was 8 torr higher than the value at their lower pH. This is equivalent to a CBF change of about 11 cc/min/100 gms.6 In addition, in their study, data were taken subsequent to an intravenous injection and a detector viewing the whole head of the dog. Since the dog has a low ratio of brain/extra cerebral tissue the data have a limited specificity for the brain (even though Carter et al. shows the concentration to be higher in brain than in scalp, skull and muscle, this is offset by the large mass of...
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