The successful use of urea in neurosurgery for the reduction of brain volume has led to many studies of the effects of hypertonic solutions of this compound upon the physiology of the intact animal. Few investigations, however, have been made of the biochemical changes which occur in the brain during and immediately following the infusion of urea. It has been considered by many authors, despite data to the contrary, that urea does not penetrate the brain and that its effects are essentially produced by its hypertonicity. The following studies were undertaken to determine the effects of urea upon the chemical constituents of the brain under conditions simulating human neurosurgery and at a time when the brain was beginning to show maximum shrinkage, i.e., 45 minutes after the beginning of the infusion of urea.

Methods

Mongrel dogs anesthetized with intravenous pentobarbital were given 1 gm./kg. of urea (30% solution) in 10 per cent invert sugar (Urevert®) over a period of 30 min. by intravenous infusion. The animals were prepared by placing polyethylene catheters in a branch of the femoral artery to facilitate the drawing of arterial blood samples and in the sagittal sinus of the brain for the removal of cerebral venous blood. A spinal needle was placed in the cisterna magna. Samples were taken before the infusion was started, 15 min. after urea had been started and 15 min. after the infusion of urea had been stopped; that is, 45 min. from the beginning of the infusion of urea. The arterial and venous blood samples were drawn simultaneously and the cerebrospinal fluid samples as quickly as possible thereafter. As soon as the last sample had been drawn the urea was washed with deionized water, dried with suction, opened and a vertical core of brain tissue extending from the cortex above to the base of the midbrain below was removed. The sample was taken immediately caudad to the cruciate sulcus and included most of the postcrucial gyrus, thus avoiding the large dorsal cerebral veins. Care was taken to remove the meninges and any visible blood. The sample from the left side of the brain was divided longitudinally, one-half being used for determinations of moisture by the conventional method of drying in a vacuum, the other half being frozen in dry ice and acetone for determinations of content of urea. The symmetrical sample from the right side was removed in a similar manner, divided in half longitudinally and frozen for the determination of sodium, potassium and chloride. The brain samples, therefore, contained similar quantities of gray and white matter. Samples of gray matter from the caudate nucleus and of white matter from the corpus callosum were also removed for analysis of urea. The blood determinations of urea and glucose were carried out by the methods of Karr and Nelson respectively. The flame photometer method was used for the determination of sodium, potassium and a modification of Whitehorn's method for the determination of chloride. The urea present in the brain tissue was determined by the method of Engel and Engel as modified by Greenberg. Standard statistical methods were used for the calculation of standard deviation and t (test for significance). The percentage of loss of water was calculated according to the formula given by Van Harreveld et al.

For comparison with the effects of urea, the biochemical changes occurring in the brain were determined after the infusion of 50 per cent solution of glucose or of a 20 per cent solution of mannitol. The glucose was infused at an average rate of 3.3 cc./min. for 30 min.; the mannitol, 0.89 gm./kg. in the same length of time. In order to separate the effects of the urea from those of...
Effects of Urea and Other Agents Upon Dog Brain

FIG. 1. Brain arteriovenous differences in blood urea during the administration of urea and of invert sugar. Cerebrospinal-fluid concentrations of urea under the same conditions. Arterial blood from the femoral artery; venous blood from the sagittal sinus.

the solution of invert sugar in which it was dissolved, the results of the infusion of the solution of invert sugar alone were assessed. In addition analyses were made of brains of animals receiving urea dissolved in physiological saline and physiological saline alone. For each of these variations the volume of solution and the rate of infusion were the same as used for urea in solution of invert sugar. The control animals received no infusion. Samples of blood and cerebrospinal fluid were taken only from the animals receiving urea in invert sugar, the solution of invert sugar alone and the control animals.

Results

The infusion of urea resulted in a high blood level of urea in 15 min. There was an arteriovenous difference in urea between the arterial blood and blood drawn from the sagittal sinus. Urea appeared in the spinal fluid more slowly and only began to approach the concentration of the cerebral venous blood about 45 min. after the urea had been started (Fig. 1). During the time that the urea was being infused there also appeared to be an increase in the amount of glucose removed from the blood in that the arteriovenous differences were greater during the infusion of the urea than before the infusion in a similar group of control animals or in animals receiving invert sugar alone (Fig. 2). The data on the loss of brain water showed that urea given in invert sugar was the most efficient way of dehydrating the brain. Next in order of efficiency were 50 per cent glucose, 20 per cent mannitol, urea in saline, saline alone and 10 per cent invert sugar (Table 1). The differences in percentage of water loss were not great in the entire series.

Although all these agents removed water from the brain, their effects upon the electrolyte content of the brain were quite different. If we consider the electrolyte data on the basis of wet weight (Table 1), we find that urea when given in invert sugar had a slight tendency to increase the level of sodium without