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Brain Water and Ion Content During Progressive Water Loading in the Newborn Puppy

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Speculation

The relative absence of apparent brain volume regulation in response to acute water loads in the newborn in comparison to the adult is due to mechanical factors, namely the more compliant newborn skull. The more compliant skull allows a greater increase in intracranial volume before intracranial pressure values are reached that are critical for pressure-dependent brain volume regulatory processes, e.g. bulk flow loss of brain ecf and CSF via arachnoid villi.

Introduction

In an earlier study (17), we observed that newborn puppies (1 - 3 days of age) had no apparent brain volume regulation when undergoing 3 h of dilutional hyponatremia. Intraperitoneal injection of a water load at a dose of 12% body weight resulted in proportional changes in plasma and brain water content without changes in brain ion content. These results differ considerably from those obtained in adult mammals exposed for similar time periods to similar stress levels (1, 2, 3, 7, 13, 16). The primary goal of the studies reported in this paper is to determine if the lack of brain volume regulation is absolute or if, with greater degrees of stress, brain volume regulation will occur, i.e., the increase in brain water content will be less than proportional to that in plasma and will be associated with changes in brain ion content.

A secondary goal is to evaluate the possible mechanical role of the rigid cranium in the volume regulatory response of the brain to hyposmotic stress. In the newborn puppy as in many other newborn mammals, the skull is less rigid due to the presence of unclosed sutures and fontanelles. If mechanical factors due to brain swelling within the rigid cranium are related to the cerebral volume regulating ionic response to water loading, in the puppy with a more compliant cranium greater degrees of brain swelling will be necessary to activate these responses. Stated as a hypothesis, as progressively greater degrees of hyposmotic stress are applied in the puppy, brain water content will increase proportionately until some critical mechanical limit is reached. At this point further stress will no longer result in proportional changes in brain swelling and brain ion loss will begin to occur. The experimental design is to produce different degrees of hyposmotic stress in newborn puppies and evaluate brain water and ion content at 3 h and intracranial pressure during the duration of the experiment.

Methods

Both mongrel and purebred beagle dogs were used for this study. Pregnant beagle dogs, purchased from Marshall Research Animals, North Rose, NY, were shipped to Hanover, NH two wks or more before the estimated delivery date. Pregnant mongrel dogs were obtained from a local animal supplier. The dogs were housed, fed, and cared for in the animal research facility at Dartmouth Medical School. After normal vaginal delivery, the experiments were performed on ten puppies greater than 6 h but less than 3 days of age, taken from four separate litters.

The general experimental strategy was to measure brain water content, intracranial pressure, and brain ion content of unanesthetized puppies exposed to 3 h of dilutional hyponatremia of different degrees produced by interperitoneal injection of distilled water. Two puppies received injections of a control dialysate (17), one being 10 ml/100 g body wt (10%) and the other being 15 ml/100 g body wt (15%). The distilled water injections were at doses of 5%, 10%, 15%, and 18% of body weight with each dose given to two puppies. Doses greater than 18% of body weight resulted in death of puppy. The injections were given after recovery from anesthesia and implantation of arterial, venous and lateral cerebral ventricular cannulae.

Surgical anesthesia was induced using 3% halothane in oxygen delivered via a small rubber cone that fit snugly over the nose and mouth of the puppy. The puppy was intubated using polyethylene tubing and the anesthetic mixture switched to 1.0% halothane, 65% nitrous oxide, and 34% oxygen. The femoral artery and vein were cannulated and arterial and central venous pressures were monitored using Statham pressure transducers and a Grass Instrument, Co., Polygraph. The puppy was placed in a small animal head holder and a midline scalp incision made. Five millimeters lateral to the saggital suture and 5 mm posterior to the coronal suture, a small hole was carefully made in the skull with a dental drill. A 22 gauge blunt needle connected to a Statham pressure gauge via saline filled polyethylene tubing was lowered into the lateral ventricle. Proper placement of the cannula was determined by visualization of variations in the intracranial pressure record due to respiratory and cardiac effects. The cannula was then fixed in place on the skull using a dental acrylic cement. The endotracheal tube was removed and the animal allowed to recover from anesthesia for 30 min. The induction of anesthesia and the intubation took 10 - 20 min and the surgery 60 - 90 min. After recovery, control values of arterial, central venous, and intracranial pressure were obtained in unanesthetized puppies breathing room air. Arterial blood was obtained and pH, PO2, and PCO2 measured on 150 µl of blood using a Radiometer BMS 3 MK2 microsystem maintained at 37.5 deg C. The body temperature of the puppies was maintained at this temperature using a Yellow Springs Instrument Proportional Temperature Controller with a small rectal probe as the temperature sensor and an infrared lamp as the heat source. The Radiometer pH electrode was calibrated with precision buffers, and the O2 and CO2 electrodes with gas mixtures of known content determined by analysis with Scholander Apparatus. Plasma bicarbonate was calculated using appropriate constants for pK' and S (19). A separate 250 µl aliquot of blood was centrifuged immediately and the plasma used for measurement of sodium and potassium by an IL43 flame photometer, chloride by Radiometer chloride titrator and osmolality by a Wescor osmometer.

After these control samples the puppy received its intraperitoneal injection. Blood, central venous and intracranial pressures were measured and recorded at 5-min intervals over the subsequent 3-h duration of the experiment. At 1 h the arterial blood gas and pH measurements were repeated and at 3 h the blood gas, pH, plasma electrolyte and osmolality measurements were repeated. The puppies were injected intravenously with sodium pentobarbital (50 mgms/kg body weight) and the whole brain was immediately removed by incising the cranial sutures. The brain was spread open by making two transverse incisions from above, one in the bisaggital plane, the other in the frontal plane. The brain surfaces were gently blotted and the brain weighed immediately. The tissue was dried to constant weight at 95 deg C and brain water content calculated from the wet and dry weights. The dried tissue was digested in 0.78 N HNO3 and the fluid analyzed for sodium, potassium and chloride content.

Results

These beagle and mongrel newborn puppies were healthy and provided a stable preparation for study. The mean ±S.D. body weight of the 10 puppies was 470 ±109 g with a range of 334 - 628 g. The individual control and 3-h values of arterial blood pressure, blood pH, blood gases, electrolytes and osmolality for each of the ten puppies in this study are shown in Table 1. The control values were in the range of values that we and others have obtained in puppies 1 - 3 days of age (11, 12, 15, 18, 19, 24). The injection of the mock plasma "control" dialysate at 10% and 15% of body weight (puppies 1 and 2) had less than a 3% effect on plasma osmolality or electrolyte values whereas injection of distilled water in increasing doses produced progressive changes in plasma osmolality and sodium and chloride concentration (puppies 3 - 10).

Plasma sodium and chloride concentration changes reflected the osmotic events. The linear regression relationship between the 3-h plasma sodium and osmolality values of all ten puppies was plasma $[Na^+]$ = 0.48 plasma osmolality -2.9, r = 0.93, whereas that for chloride was plasma $[Cl^-]$ = -0.40 plasma osmolality -14.6, r = 0.95. The plasma potassium concentration increased in all animals during the 3-h experimental period ranging from 4.2 to 4.7 mmole/liter in 8 animals and increasing to 7.6 and 8.3 mmole/liter in 2 animals. In the six most severely stressed animals, puppies 5 - 10, there was a tendency for the development of a metabolic acidosis. This acidosis was mild in puppies 5, 7, 8, and 9 and more severe in puppies 6 and 10 with plasma bicarbonate concentrations at 3 h compared with control being decreased 11.1 and 16.6 mmole/liter. Puppies 6 and 10, with the larger changes in plasma bicarbonate, had the more severe elevations in plasma potassium.

The changes in PaCO2 and PaO2 in the 10 puppies during the course of the experiment were quite variable, ranging from +20 to -29 mmHg for PaCO2 and +31 to -23 mmHg for PaO2. The two most acidotic animals had the lowest PCO2 values. Arterial pH decreased in 7 of the 8 water-loaded puppies with the range of the final values being 7.020 to 7.370. Mean arterial blood pressure also showed a tendency in some animals to decrease during the 3-h water loading experiment although the blood pressure changes were variable.

The brain water and ionic content and CSF pressure of the control animals and in response to progressive water loading in the experimental animals are shown in Table 2 and Figures 1-3. The brain water content expressed as ml water per g dry brain wt (Fig. 1) increased progressively with the increase in plasma water as indicated by plasma osmolality (Table 2) or the % decrease in plasma osmolality (Fig. 1). For up to a 12% decrease in plasma osmolality the increase in brain water content was quite close to the line representing a proportional response. The brain water content of the puppies with decreases of plasma osmolality greater than 15% were well to the right of the proportionality line, a response consistent with the idea that there is some threshold value of water-loading stress beyond which some apparent brain volume regulation does take place. It is important to note that attempts in two puppies to induce changes in plasma osmolality of greater than 18% resulted in death of the puppy within the first 2 h of the protocol. Unfortunately we did not measure brain water or ionic content in these puppies.

The brain sodium, chloride, and potassium ion responses are shown in Table 2 and in Figure 2 expressed as meq ion/kg dry brain wt versus the % decrease in plasma osmolality. Brain sodium and chloride content did decrease as the water loading stress was increased (Table 2 and Fig. 2). The slopes of the linear regression of the relationships in Figure 2 for sodium and chloride differed from the null hypothesis of a slope = 0 at a confidence level of $P < 0.03$ for sodium and $P < 0.001$ for chloride. Brain potassium content did not decrease significantly (Table 2 and Fig. 2).

The response of CSF pressure measured in the right lateral cerebral ventricle during the 3-h duration of the experiment is shown in Figure 3. With increasing water loads there is a progressive increase in peak CSF pressure, in the CSF pressure levels during the postpeak decline, and in the total pressure-time integral. The time to peak pressure was approximately the same in each case, 40-45 min. The relationship of peak CSF pressure to the % decrease in plasma osmolality was linear, y = 8.69x + 85.9, r = 0.96. The relationship of mean CSF pressure to the % decrease in plasma osmolality was also linear, y = 5.3x + 69.1, r = 0.97.

Discussion

The initial control mean blood pressure, plasma electrolyte, and osmolality values of the ten unanesthetized puppies of this study, breathing room air, agree quite closely with previously published values obtained in unanesthetized or lightly anesthetized newborn puppies (11, 12, 15, 18, 19, 24). The intraperitoneal injection of distilled water at doses of 5-18% of body wt produced the desired effects on plasma osmolality and electrolytes but also appeared to alter, in some animals, blood pressure and acid-base balance. There was a tendency for the plasma bicarbonate concentration and the mean blood pressure to decrease in some of the severely water loaded animals. We were unable to demonstrate a statistically significant dose-response relationship between the fall in plasma osmolality and the degree of acidosis or hypotension. The two most severely acidotic and hypotensive puppies, 6 and 10, did not have the most severe degree of hyposmolality (Table 2); however, water loads greater than 18% of body weight did result in severe hypotension, acidosis and death in two puppies that are not included in this report. This study then entails the use of water loads that range into the stress level that can result in hypotension and acidosis in some puppies. We included all puppies in the study that survived the 3-h experimental period.

The major reason for this study grew out of the observation in this laboratory that 3 h of water loading at a dose of 12% body weight results in a proportional change in plasma osmolality and in brain water content and an absence of any loss of brain sodium, chloride, or potassium (17). Apparent brain volume regulation as evaluated by measurement of brain water content during acute water loads was absent in the newborn puppy (17), a finding that is in marked contrast to the observations made in adult mammals exposed to similar degrees of water loading over similar time periods (1, 2, 3, 7, 13, 16). In the adult, the ratio of the fractional change in brain water content to the fractional change in plasma osmolality ranges from 0.37 to 0.56 (1, 2, 3, 7, 13, 16), values far below the value of 1.0 observed in the puppy (17). Associated with this apparent brain volume regulation there are losses of brain tissue sodium, chloride, and potassium (1, 2, 3, 10, 13, 14, 16) that are thought to indicate the presence of ionic extrusion mechanisms involved in the regulation of brain volume.

In this study we used progressively greater water loads to evaluate via a dose-response approach whether or not the absence of brain volume regulation in the newborn puppy is an absolute failure or if, with greater stress levels, some brain ion loss and associated volume regulation might become apparent. With water loads up to the level of our previous study (12% body wt) the brain water content increased progressively and in each case was quite close to the predicted proportional brain water content response (Fig. 1). The newborn puppy brain in this range of water loads behaves as a passive osmometer: swelling in proportion to the osmotic stress. This is a finding that confirms our earlier observations. With water loads greater than 12% of body weight, however, brain water content increased less than the proportional response prediction. At severe stress levels some apparent brain volume regulation does take place although even in this case the ratio of the fractional change in brain water content to the fractional change in plasma osmolality is 0.65 - 0.70, values still higher than those reported in adult mammals, 0.37 - 0.56.

Linear regression analysis of the ionic responses of the newborn puppy brain to the progressive water loads (Fig. 2) shows that there is no significant loss of brain potassium, a predominantly intracellular ion, but that there is a statistically significant change from zero in the slope of the regression of brain sodium and chloride versus the degree of plasma hyposmolality. This analysis indicates that brain sodium and chloride loss can occur in response to water loading in the newborn puppy and suggests that it occurs progressively as plasma osmolality is decreased below the normal value. In our earlier study we observed no significant change in brain tissue sodium or chloride content after 3 h of a water load of 12% body weight (17). But in this earlier study only a small piece of cerebral tissue was used for analysis whereas in the present work the entire brain was analyzed; thus, part of the difference between the brain sodium and chloride changes in this study compared to our previous study could reflect regional differences in brain response. A second difference between this and our previous study is the presence of acidosis and hypotension that developed during the water load in some animals of this study. The two animals with the most severe changes in pH and blood pressure, puppies 6 and 10, did not show the greates changes in brain tissue sodium or chloride nor did they suffer from the largest hyposmotic stress (Table 2). Although water loading can cause hypotension and acidosis in some puppies, the presence of acidosis and hypotension does not seem to enhance the loss of ions by the brain in response to the water load. We conclude that with progressively severe acute water loads: (1) there is a significant loss of brain tissue sodium and chloride in the newborn puppy; (2) that this ion loss is greater as the water load is greater; and (3) that this ion loss contributes to the processes that diminish the increase in brain water content that occur with acute water loads greater than 12% body weight. Because sodium and chloride are predominantly extracellular fluid ions, the effects of changes in brain content of these ions must predominantly involve changes in this space. It is important to remember that the newborn in comparison to the adult brain has a high water content (4, 9, 14, 17, 19). In response to a 12% water load, the ecf space of the newborn puppy increases whereas in the adult the ecf space decreases (13, 16, 17). Both the inability of the newborn puppy to show evidence of apparent brain volume regulation at 12% or lower water loads as well as the ability to do so at greater stress levels may revolve around the regulation of the brain ecf space.

The mechanisms involved in the brain ecf response to water loading in the adult are unknown. In general, sodium and chloride could diffuse or be transported by a carrier-mediated process from brain to blood accompanied by water, or brain ecf could move via bulk flow into CSF and exit via the CSF pressure-dependent bulk flow process. With respect to diffusion or ion transport, the notion that blood-brain barrier function may be immature in the newborn is now subject to question (5, 23) although no specific blood-brain barrier sodium or chloride efflux mechanisms have been described in adult or newborn. The loss of brain sodium and chloride at water load dose levels (below 12% body wt) which are associated with increases in brain water content that are proportional to the water load, is consistent with diffusional or carrier-mediated ion loss not associated with water. Bulk flow of brain ecf in the adult has been demonstrated (6, 21), a process that is enhanced by osmotic stress (21, 25) and is thought to be involved in the resolution of vasogenic brain edema (20). In the newborn brain with an ecf space roughly twice that of the adult (9, 17) it is reasonable to presume that ecf bulk flow might be prominent. Although we can make no firm conclusion from our data concerning the mechanism of brain sodium and chloride loss in the severely water-loaded puppy, analysis of the CSF pressure responses (Fig. 3) together with the brain volume changes is of interest in respect to the possibility of bulk flow brain ecf loss via CSF.

The CSF pressure in puppies increased to higher peak and sustained values as the water load dose increased (Fig. 3). The peak pressure occurred between 40-50 min at each dose, the CSF pressure then gradually declined. The peak hydrostatic pressure levels attained are at least an order of magnitude too small to offset the osmotic forces present with the water load but are sufficient to increase bulk flow CSF loss via normal CSF drainage pathways. In Figure 1 we have shown that at water loads up to 12% of body weight the response of brain water content is predictable by the osmotic gradient and appears to be passive. In this stress range, brain water content can increase no further and it is reasonable to presume that the increase has occurred within the first 40-50 min in close association with the peak CSF pressure. After this time, CSF pressure declines whereas brain water content stays the same, a result that indicates either a decrease in the size of the CSF or blood compartment or an increase in the intracranial compliance. If at these lower water load levels some large cavity CSF is lost (an event which would not affect our tissue ion measurements) then with greater stress, greater large cavity CSF loss could also be associated with brain ecf loss via a bulk flow mechanism. It is puzzling, however, why some brain ecf loss is not lost via this mechanism even at the lower stress levels given the large ecf space in the newborn brain which is contiguous with the large cavity CSF spaces. It may be that bulk flow loss of brain ecf via the CSF requires intracranial pressure levels produced only by high dose water loads in newborn animals. An analysis of intracranial pressure gradients at different water loads in animals with rigid and non-rigid skulls would help to answer this question. An alternative to this mechanical explanation is that higher water load doses could also alter ionic diffusion or transport processes at the blood brain barrier.

The results of this study modify only slightly the conclusions of our earlier work. The newborn puppy is capable of showing some apparent brain volume regulation in acute dilutional hyponatremia. The regulation is due to loss of sodium and chloride but not potassium and occurs only at rather severe stress levels. Whether this less than adult-like regulation is harmful to the animal or whether better regulation occurs with more chronic stress remains to be seen. It is conceivable that the greater increases in brain ecf volume in the water loaded puppy do little damage to neuronal function until some critical intracranial pressure is reached.

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Table I. Initial control and final 3h values of blood pressure, acid-base balance, electrolytes and osmolality for the ten puppies of the study.

N	Condition		MAP mmHg	pH	P_{CO_2} mmHg	P_{O_2} mmHg	HCO_3^- mmol/l	Na^+ mmol/l	K^+ mmol/l	Cl^- mmol/l	Osm. mosm/l
1	Control (10% injection)	C	63	7.295	42	59	20.5	139	4.5	102	297
		3h	40	7.310	38	57	19.2	143	4.7	109	296
2	Control (15% injection)	C	73	7.434	34	52	22.8	141	3.8	103	300
		3h	70	7.358	42	49	23.7	145	4.5	107	305
3	5% H_2O	C	63	7.440	34	49	22.5	142	4.1	108	300
		3h	60	7.370	42	51	24.3	136	4.5	99	277
4	5% H_2O	C	75	7.550	26	42	22.8	140	4.2	100	300
		3h	70	7.361	46	47	26.1	132	4.6	95	279
5	10% H_2O	C	63	7.325	38	31	19.9	141	4.1	104	300
		3h	60	7.359	31	28	17.5	126	4.4	93	276
6	10% H_2O	C	50	7.358	41	51	23.1	141	2.9	102	291
		3h	30	7.180	32	28	11.1	126	8.3	92	275
7	15% H_2O	C	63	7.539	29	40	24.8	139	3.7	101	299
		3h	63	7.360	43	50	24.3	118	4.2	85	252
8	15% H_2O	C	55	7.539	29	36	24.9	140	4.0	103	304
		3h	48	7.379	40	67	23.7	121	4.2	86	250
9	18% H_2O	C	55	7.313	39	57	19.8	139	3.8	102	290
		3h	68	7.292	34	39	16.5	115	4.3	83	238
10	18% H_2O	C	78	7.295	40	41	19.5	139	4.3	105	296
		3h	45	7.020	11	57	2.9	117	7.6	92	262

Table II. Brain water and electrolyte content for the ten puppies of the study.

N	Condition	plasma osmolality mosm/l	brain water ml/g dry wt.	sodium meq./kg dry wt.	potassium	chloride
1	Control	296	8.12	657	634	476
2	Control	303	8.24	681	639	492
3	5% H_2O	277	8.66	623	628	440
4	5% H_2O	279	8.83	673	619	467
5	10% H_2O	276	8.94	668	632	479
6	10% H_2O	275	8.68	711	667	480
7	15% H_2O	252	9.09	629	638	402
8	15% H_2O	250	9.09	635	624	431
9	18% H_2O	238	9.38	590	590	400
10	18% H_2O	262	9.20	646	639	457

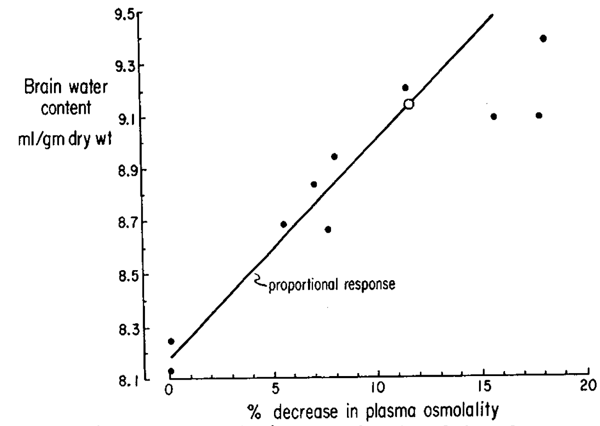

Figure 1. Brain water content is shown as a function of the % decrease in plasma osmolality for ten newborn puppies (●). The % decrease in osmolality is calculated for each puppy using its control and final (3 h) plasma osmolality values and the relationship: (control osmolality - test osmolality)/control osmolality. The line drawn on the figure represents the response of brain water content proportional to the plasma osmolality change. This was calculated using the mean brain water content value of the two control puppies for comparison to individual test values. The open circle (o) represents the mean % increase in brain water as a function of the % decrease in plasma osmolality for the puppies of our previous report (17).

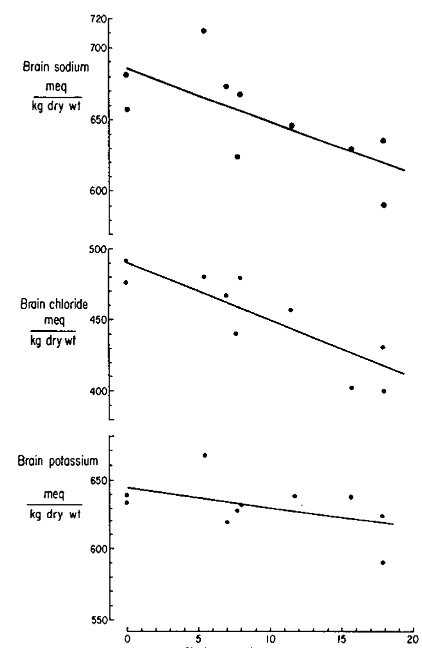

Figure 2. Brain sodium and potassium content are shown as a function of the % decrease in plasma osmolality for 10 newborn puppies. The lines on each panel represent the least-squares linear regression of these data. The equation for the sodium line is $y = -3.61x + 684$, $r = 0.69$, $P < 0.026$. For chloride, the equation is $y = -4.39x + 491$, $r = -0.87$, $P = 0.001$. For potassium the equation is $y = -1.44x + 644$, $r = 0.49$, $P = 0.15$.

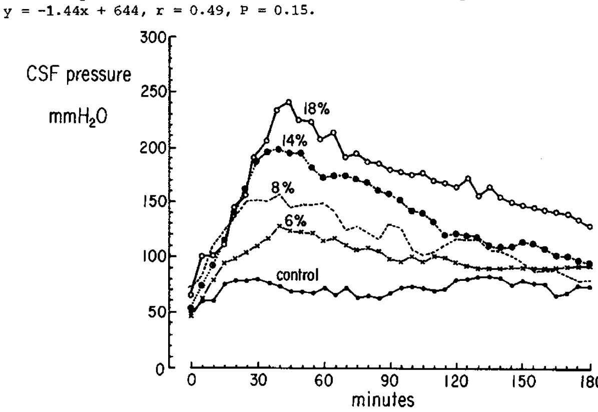

Figure 3. Cerebrospinal fluid pressure measured in the right lateral ventricle is shown as a function of time. Values recorded at 5-min intervals during the duration of the experiments are shown. For simplification the mean value of the two puppies in each group are plotted. The % values on the figure represent the % decrease in mean plasma osmolality in each group.

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