Effects of Centraly Administered Arginine Vasopressin and Atrial Natriuretic Peptide on the Development of Brain Edema in Hyponatremic Rats

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Introduction

Centrally released arginine vasopressin (AVP) and atrial natriuretic peptide (ANP) have been shown to participate in the regulation of the water homeostasis of the central nervous system (CNS). Brain water accumulation has been shown following the central administration of AVP whereas reduced cerebral water and sodium content has been reported in response to centrally administered ANP. The opposite volume regulatory effect of AVP and ANP has been confirmed also at the cellular level, where vasopressin has been shown to increase, whereas ANP has been shown to decrease glial cell volume in astroglial cultures. Diffusion Weighted Imaging (DWI) has proven to be a powerful non-invasive tool in investigating tissue microstructure and in obtaining information about changes in cellular volume fraction, extracellular and intracellular water diffusion coefficients. Changes in the Apparent Diffusion Coefficient (ADC) are thought to reflect combined effects of changes in cellular volume fraction, extracellular tortuosity and intracellular diffusion coefficient. It has been suggested that the decrease of ADC may reflect cellular swelling (cytotoxic edema), whereas increased ADC values have been associated with increased extracellular to intracellular volume fraction ratio and the development of vasogenic brain edema.

In the present study, we evaluated the role of centrally administered AVP and ANP in the control of brain cell volume during the development of cerebral edema associated with severe acute systemic hyponatremia. Changes in the extra/intracellular compartment ratio were estimated as changes in the ADC of the brain tissue, determined by DWI. An attempt was made to assess the dynamic changes in the intra and extracellular compartments of the cerebral tissue in response to intraventricular AVP or ANP administration.

Methods

Studies were performed on male Wistar rats weighing 250-300 g. The animals were assigned to three experimental groups. The intracerebroventricular (icv.) administration of 120 µg AVP (AVP group, n=5), 20 µg ANP (ANP group, n=5) or 4 µl physiological saline (saline group, n=6) were performed into the right lateral ventricle.

MR imaging was performed on a 7T MRI system (Varian Inc., Palo Alto, Ca), equipped with self-shielded gradient-coils. Initially, baseline T1 and DWI scans were obtained, which was followed by the icv. injection of the drugs and the animal was reinserted into the magnet. For both sequences we used 7×7 cm FOV, 128×128 data matrix and NEX=1. DWI parameters were b=0 and 1400 cm/s2, TE=50 ms and TR=1200 ms. T1 parameters were TI=50-1000 ms, TE=12 ms and TR=1050 ms. ADC and T1 maps were calculated on a pixel-by-pixel basis. Two DWI scans were performed 6 and 18 minutes after the icv. injection. Following the DWI scans, systemic hyponatremia was induced by intraperitoneal (ip.) administration of 140 mmol/l dextrose, corresponding to ~20% of the body weight. Immediately after the ip. injection, the animals underwent 6 subsequent DWI scans in 18 min intervals. An additional T1 measurement was finally performed. At the conclusion of the imaging procedure venous blood was taken for assessment of serum osmolarity and sodium concentration, the animal was sacrificed, the brain was removed and total brain water content was determined by the dry/wet method. *In vivo* brain water content determination was performed as described by Fatouros et al, using the T1-maps calculated from the T1 weighted images.

Results

Establishment of hyponatremia. The intraperitoneal administration of hypotonic dextrose solution induced a marked fall in serum osmolarity from 310 ± 2 mOsm/l to 275 ± 3, 277 ± 2 and 272 ± 4 mOsm/l in the icv. saline, AVP and ANP group, respectively. This decrease was paralleled by reduced serum sodium values from 146 ± 1 mmol/l in controls to 110 ± 1 mmol/l in the saline, 111 ± 3 mmol/l in the AVP and 112 ± 2 mmol/l in the ANP group. There was no significant difference in the serum parameters between the experimental groups, indicating that the centrally administered AVP and ANP did not have any periferial effects on the serum osmolarity.

Changes in brain water content. By the end of the hydration protocol, the tissue water content of the total brain, measured by the dry/wet method, increased from 78.3 ± 0.2% measured in nontreated controls to 79.6 ± 0.2%, 80.2 ± 0.0% and 79.4 ± 0.1% in the saline, AVP and ANP groups, respectively. The results of the *in vivo* water content measurements, calculated from the T1-water maps were congruent and significantly correlated (r=0.72, P<0.002) to the data obtained by the wet/dry method, revealing an increased tissue water content from 78.0 ± 0.2% before the start of the experimental protocols to 78.9 ± 0.2% in the saline, 79.7 ± 0.2% in the AVP and 78.6 ± 0.1% in the ANP group. The brain water content in the AVP group at the end of the hydration protocol was significantly higher compared to that of the saline group (P<0.015 by the dry/wet method and P<0.032 by the T1-water maps).

ADC changes. The time course of the changes in ADC is shown in Fig. 1. There was no change in the ADC in response to the icv. saline or AVP injection (Fig. 1A), whereas icv. ANP induced a rapid, significant ADC increase to 111.5 ± 3.1% (P<0.003) and 109.5 ± 2.0% (P<0.03) of the baseline level 6 and 18 minutes following the icv. injection, respectively (Fig. 1B). Twenty-four minutes after the start of hyponatremia, a rapid ADC decrease to 92.5 ± 2.5% of the baseline value could be observed in the saline group, followed by a gradual decrease to 89.8 ± 1.9% at 96 minutes (Fig 1). The initial ADC changes after the induction of hyponatremia in the AVP group were similar to the saline group, with a rapid decrease to 92.3 ± 2.4% and 90.2 ± 2.3% after 24 and 42 minutes of hypoosmolarity, respectively. However, the reduction in the ADC became significantly more pronounced compared to the saline group to 85.2 ± 1.6% (P<0.008), 83.3 ± 1.6% (P<0.001) and 83.3 ± 1.8% (P<0.02) at 60, 78 and 96 minutes after the onset of hyponatremia, respectively (Fig 1A). In the ANP group, despite the rapid decrease of the ADC following the onset of hyponatremia, in the initial one hour the values (104.7 ± 3.3%, 99.0 ± 1.7% (P<0.032), 99.4 ± 2.4% and 93.2 ± 2.3% at 6, 24, 42 and 60 minutes, respectively) were consistently higher than those observed in the saline group, decreasing finally to 88.5 ± 2.6% and 86.9 ± 2.4% at 78 and 96 minutes, respectively (Fig 1B).

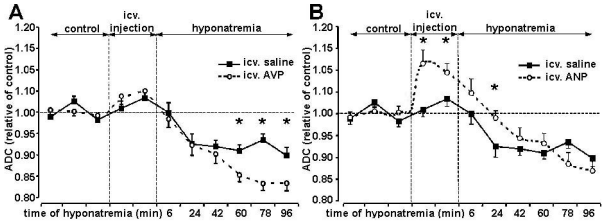

Figure 1. Comparison of the time course of ADC changes in the saline and AVP (A) or ANP (B) groups.

Discussion

Our data indicate that in systemic hyponatremia, the central administration of AVP results in a delayed, more pronounced cellular swelling, presumably by inhibiting the regulatory volume decrease (RVD) response. In contrast, centrally administered ANP promptly reduces the intracellular space, this effect, however is short lasting and can not inhibit the development of cytotoxic brain edema in systemic hyponatremia.

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