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Activity of the renin–angiotensin–aldosterone system in full-term newborn infants during the first week of life

By

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A study was performed in 7 healthy full-term newborn infants with mean birth weight of 3130 g (range, 2650—2850 g) and a mean gestational age of 38.8 weeks (range, 37—41 weeks) to investigate the postnatal changes of plasma renin activity (PRA), plasma aldosterone concentration (PA) and urinary aldosterone excretion (UAE) in relation to electrolyte balance.

PRA, PA and UAE fell significantly from their initially high values of 28.36 ± 3.6 ng/ml/hr, 1.5 ± 3 ng/ml and 7.1 ± 1.9 μg/day on the first day to 6.84 ± 2.9 ng/ml/hr ($p < 0.01$), 0.71 ± 0.1 ng/ml ($p < 0.01$) and 5.5 ± 1.6 μg/day ($p < 0.05$), respectively, on the 5th day.

No significant correlation was found between either PRA and PA or PA and UAE. PRA and UAE showed a significant negative correlation with dietary sodium intake, the other parameters of sodium and potassium homeostasis, however, had no apparent influence on the activity of RAAS.

The initial high level and the rapid postnatal decline in RAAS activity has been attributed to perinatal stress imposed by labour and delivery and not to the changes in sodium or potassium balance in the early days of life.

The levels of various components of the renin–angiotensin–aldosterone system (RAAS) are all raised in the immediate neonatal period. Plasma renin activity (PRA) [6, 11, 12, 14], plasma angiotensin II [3] and plasma aldosterone concentration (PA) [2, 6, 12, 20, 25, 26] are high in newborn infants and decrease progressively with advancing age.

The reason for the increased RAAS activity during the neonatal period is not clear. Perinatal stress imposed by labour and delivery [3, 6, 11, 16, 18], low systemic blood pressure [3], negative salt balance [29, 30] renal tubular unresponsiveness to aldosterone [10, 27], stimulation by increased sympathetic activity [15, 19] or by increased endogenous prostaglandin production [31] and the low rate of metabolic clearance of renin [28] and aldosterone [20, 29] have all been implicated as possible factors.

The physiological role and clinical significance of the high activity is not understood. Evidence is, however, accumulating to indicate that in the neonate RAAS may be of great importance in the maintenance of blood pressure [4, 24], blood volume [7] and sodium homeostasis [29, 30]. More-

over, it has been shown that in spite of its high baseline activity, the neonatal RAAS is readily responsive to changes in blood volume [7], alterations in sodium balance [29, 30, 33] or pharmacological stimulation [22, 33].

The present study was performed in healthy full-term newborn infants during the first week of life to investigate the postnatal changes of PRA, PA and UAE. Some parameters of sodium and potassium balances were also examined to see what effect, if any, these parameters might have on the postnatal development of RAAS activity.

Material and Methods

Studies were carried out in 7 healthy male full-term newborn infants with a mean birth weight of 3130 g (range, 2650—3850 g) and with a mean gestational age of 38.8 weeks (range, 37—41 weeks). All infants were born vaginally after uncomplicated pregnancy. The mothers were on a normal diet without diuretic therapy. No sign of perinatal asphyxia was observed and all infants remained well during the whole period of study. They were fed with 5% glucose solution from the 12th to the 24th hour of life and were breast fed from the 2nd day after delivery. The daily milk intake increased gradually to attain a volume of 150—180 ml/kg by the end of the first week.

The plasma level, the intake and urinary excretion of sodium and potassium, as well as PRA, PA and UAE were determined on the 1st, 3rd and 5th days of life.

Urine was collected fractionally over a period of 24 hours. The specimens were refrigerated, pooled and stored at −20 °C until analysed. Blood samples were taken from a scalp vein at 9.00 a.m., at least 2 hours after the last feeding. The infants were kept supine for a period of 1—3 hours before blood sampling.

PRA was measured radioimmunologically according to the method of Haber et al. [13] using SORIN-CEA-IRE-RENK kits. Aldosterone concentration in plasma and urine was also determined by RIA [34] using SORIN-CEA-IRE-ALDOK kits. Plasma, milk and urinary sodium and potassium concentration measurement was made by flame photometry.

Statistical analysis was performed by calculating the coefficient of correlation, the equation of regression and Student's t test.

Results

Intake, urinary excretion, retention rate and plasma concentration of sodium and potassium are shown in Fig. 1 as a function of postnatal age. It can be seen that sodium intake markedly increased from the very low value of 0.13 ± 0.09 mEq/kg/day on the 1st day to 1.16 ± 0.10 mEq/kg/day on the 3rd day ($p < 0.01$) and to 1.46 ± 0.10 mEq/kg/day ($p < 0.05$) on the 5th day of life. Urinary sodium excretion was low and did not vary considerably until the 3rd day but then it rose significantly to a value of 1.0 ± 0.29 mEq/kg/day ($p < 0.05$) by the 5th day. As a result, a positive sodium balance could be established on the 3rd to 5th days with a sodium retention rate of about 0.5 mEq/kg//day. At the same time plasma sodium concentration also increased from 143.7 ± 1.6 mEq/l on the 1st to 148.2 ± 3.6 mEq/l on the 5th day of life ($p < 0.05$).

A similar pattern was observed for the intake and retention rate of potassium. The urinary potassium excre-

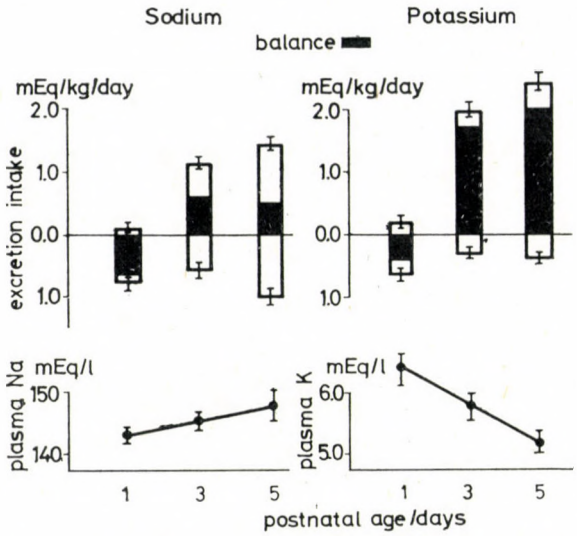

FIG. 1. Sodium and potassium balances in full-term newborn infants during the first week of life

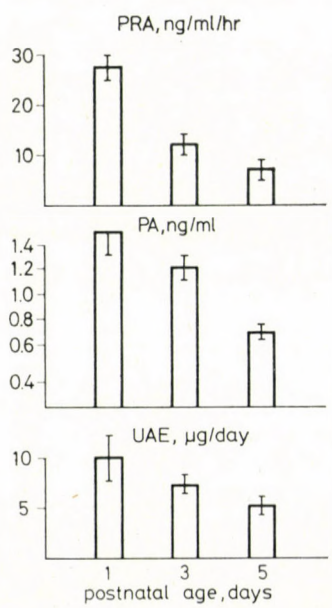

FIG. 2. PRA, PA and UAE in full-term newborn infants during the first week of life

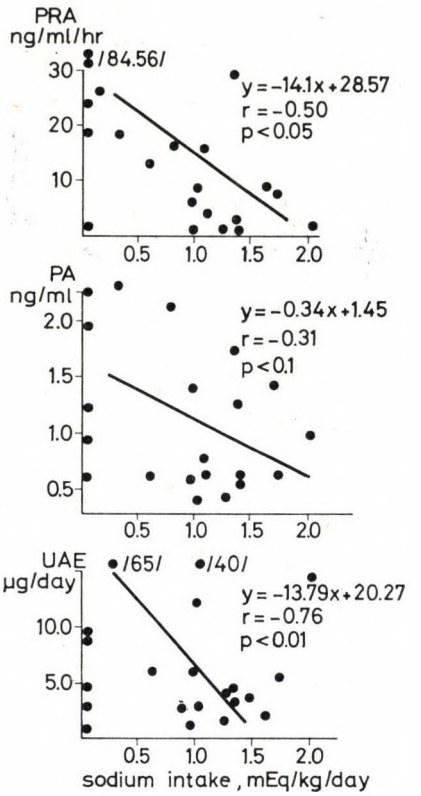

Fig. 3. Sodium intake and PRA, PA and UAE in full-term newborn infants during the first week of life

tion declined, however, significantly from 0.64 ± 0.11 on day 1 to about 0.35 mEq/kg/day on day 3—5. ($p < < 0.05$). Plasma potassium concentration decreased gradually with advancing postnatal age from 6.42 ± 0.42 mEq/l on the 1st to 5.22 ± 0.3 mEq/l on the 5th day ($p < 0.01$).

Figure 2 demonstrates the changes in PRA, PA and UAE with increasing postnatal age. As it is seen, PRA was the highest on the 1st day ($28.36 \pm \pm 3.6$ ng/ml/hr) and it gradually fell to the value of 6.84 ± 2.9 ng/ml/hr by the 5th day of life ($p < 0.01$). Essentially the same developmental pattern was found for PA and UAE. Both declined steadily from their peak values of 1.5 ± 0.3 ng/ml and 7.1 ± 1.96 µg/day on the first day to 0.71 ± 0.1 ng/ml $p < < 0.01$) and 5.5 ± 1.6 µg/day ($p < < 0.05$), respectively, on the 5th day of life.

Although the trend and time course of the postnatal development of these hormone values were quite similar, PRA did not correlate significantly with PA. No correlation could be found between either PRA and UAE, or PA and UAE.

In search of the relationship between electrolyte status and the function of RAAS, it was observed that PRA and UAE were inversely related to sodium intake (Fig. 3).

Neither sodium balance, renal sodium excretion, nor the urinary sodium/potassium ratio correlated significantly with PRA, PA and UAE. Plasma potassium, however, showed a week positive correlation with PRA (r: 0.38, $p < 0.05$), but no correlation was found between plasma potassium and PA or UAE.

The activity of RAAS was independent of the changes in body weight. Body weight on the 1st, 3rd and 5th days was 3130 $\pm$ 83 g, 3041 $\pm$ 183 g and 3080 $\pm$ 200 g, respectively.

Discussion

The results of the present study are consistent with those obtained by others [2, 3, 6, 11, 12, 14, 20, 25, 26] showing that PRA and PA are high in newborn infants for a few hours after birth and then they decline progressively by the end of the first week of life.

On the basis of these observations the possibility arose that the high activity of RAAS in the immediate neonatal period may be attributed to the stressful stimulation imposed by labour and delivery. This is supported by the facts that catecholamines in cord blood were found to be elevated in infants born vaginally [15, 19] and that the neonatal juxtaglomerular apparatus is hypersensitive to adrenaline [9]. Maternal treatment with betamimetic drugs to prevent premature delivery also resulted in enhanced PRA [8].

The increased endogenous prostaglandin production during labour may also be involved in the neonatal hyperactivity of RAAS [31]. Elective Caesarean section and indomethacin administration to the mother are known to prevent the physiological rise in endogenous prostaglandin production, and this results in a lowering of PRA and plasma angiotensin concentration, and PA in cord blood [3, 6, 11, 16, 18, 21].

In agreement with some recent reports [2, 6, 12, 20, 25, 26], PA of the newborn was also found to be elevated on the first days after birth. Since no correlation was observed between PRA and PA, the primary role of the renin–angiotensin system in regulating aldosterone production is questioned and other factors are to be considered.

Hyperkalaemia [17] and ACTH have a direct stimulatory effect on the zona glomerulosa and may contribute to the elevation of PA. In newborn lambs a significant adrenal aldosterone response occurred after KCl infusion [23] and hyperkalaemia may be assumed to exert a similar effect in the neonate. We have, however, failed to demonstrate a correlation between the plasma potassium level and the aldosterone status, confirming the observation by Siegel et al [25] who noted a dissociation between plasma potassium and aldosterone during the first days of life.

In support of the role of ACTH in the control of aldosterone production

in newborn infants, it can be regarded as an indirect evidence that infants born after normal labour have, due to stress, a higher plasma ACTH level than those delivered by Caesarean section [1].

The postnatal development of RAAS activity might also be expected to relate to the changes in sodium homeostasis. We could show [29, 30] that in preterm infants the low dietary sodium intake, the high rate of urinary sodium excretion and the subsequent negative sodium balance and hyponatraemia resulted in a marked postnatal increase in PRA, PA and UAE. Supplemental sodium then prevented the increase in the activity of RAAS [33]. Similarly, Godard et al found that in full-term infants PRA correlated inversely with sodium intake and urinary sodium [12], while a similar inverse relationship was not found for plasma aldosterone by Siegel et al [21] and Raux-Eurin et al [20] after intake of 0.3—4.5 mEq/kg/day of sodium.

In the present study a significant negative correlation was found between PRA, UAE and sodium intake, while the function of RAAS was independent of the other parameters of sodium homeostasis.

The initial high level and the rapid postnatal decline in the activity of RAAS can mainly be attributed to perinatal stress imposed by labour and delivery. The dissociation between sodium balance and PRA, as well as between PRA, plasma potassium level and aldosterone status, may reflect the rapid changes in blood pressure, blood volume and renal blood flow rather than the lack of renin release and adrenal aldosterone production in response to stimulation.

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