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The Influence of NaCl Supplementation on the Postnatal Development of Urinary Excretion of Noradrenaline, Dopamine, and Serotonin in Premature Infants

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ABSTRACT. The present study was designed to investigate the role of noradrenaline (NA), dopamine (DA), and serotonin (5-HT) in the adaptation of premature infants to alterations of sodium balance. Urinary excretion of NA, DA, and 5-HT was measured spectrofluorimetrically in a group of low birth weight premature infants with (group S) and without (group NS) NaCl supplementation. Group NS consisted of 10 infants with a birth weight of 1200–1750 g (mean, 1493 g) and gestational age of 28–31 wk (mean, 30.1 wk). Group S included 10 infants with mean birth weight of 1414 g (range, 1150–1600 g) and mean gestational age of 30.5 wk (range, 27–32 wk). Measurements were made on the 7th day and weekly thereafter until the 5th wk of life. NaCl supplementation was given in a dose of 3–5 and 1.5–2.5 mEq/kg/day for 8–21 and 22–35 days, respectively.

In group NS, mean urinary excretion of NA and DA increased from 8.6 ± 1.5 and 15.8 ± 2.4 μg/day to maximum values of 21.4 ± 5.5 ($p < 0.05$) and 33.4 ± 6.0 μg/day ($p < 0.01$) in weeks 2–3, respectively. 5-HT excretion averaged about 60 μg/day and showed no consistent change during the course of the study.

NaCl supplementation prevented the rise of NA and DA excretion above the initial baseline values. The postnatal course of 5-HT excretion, however, remained unaffected by NaCl supplementation. Urinary excretion of NA in weeks 2–3 ($p < 0.05$) and DA in weeks 2–4 ($p < 0.05$) were significantly lower in group NS. (*Pediatr Res* 19: 5–8, 1985)

Abbreviations

RAAS, renin-angiotensin-aldosterone system
NA, noradrenaline
DA, dopamine
5-HT, serotonin
CA, catecholamine
VMA, vanillylmandelic acid

Recent studies have shown that renal salt wasting frequently seen in low birth weight premature infants results in negative sodium balance and hyponatremia which may last for several weeks (3, 10, 16, 26, 27, 31). In response to the sodium-depleted state, adaptive endocrine changes occur to restore sodium balance. Renal immaturity, however, impairs efficient tubular sodium reabsorption so that the correction of sodium depletion and hyponatremia may require a long period of time (16, 32–34).

In view of the adverse clinical effects of hyponatremia (1, 7, 8, 34), sodium supplementation has been proposed to help ensure optimal sodium balance (1, 34). Additionally, this therapeutic measure has been found to provide a useful approach to assessment of the endocrine reactions of preterm neonates induced by salt depletion. Using this experimental approach, we have demonstrated the importance of the RAAS (34), prostaglandins (11), and prolactin (12) in the adaptation of premature infants to the alterations of sodium balance.

Substantial evidence has accumulated to indicate that the sympathetic nervous system and some major neurotransmitters also are involved in the renal control of sodium homeostasis. Namely, NA has been demonstrated to enhance renal tubular sodium reabsorption, while DA has been claimed to inhibit renal tubular sodium transport and to cause natriuresis (2, 5). Moreover, there is some evidence although inconclusive, to suggest that 5-HT produces antidiuresis and antinatriuresis (23).

On the basis of these clinical and experimental observations, we assessed the possible involvement of NA, DA, and 5-HT in the control of sodium balance in healthy premature infants during the first 5 wk of life.

MATERIALS AND METHODS

The same experimental protocol was applied as in our previous studies. Urinary excretion of NA, DA, and 5-HT was compared in a group of healthy premature infants fed breast milk (group NS) with that of premature infants of similar birth weight and gestational age who were given NaCl supplementation (group S) (11, 12, 34). The infants were randomly selected for one of the two groups. Group NS consisted of 10 infants with a birth weight of 1200–1750 g (mean, 1493 g) and gestational age of 28–31 wk (mean, 30.1 wk). Group S included 10 infants with mean birth weight of 1414 g (range, 1150–1600 g) and mean gestational age of 30.5 wk (range, 27–32 wk).

All infants were delivered vaginally after an uneventful prenatal history and an uncomplicated labor. None of the mothers received β-mimetic drugs or steroids. The infants had Apgar scores of 7 or more at 1 min and remained well during the entire period of the study. No clinical or laboratory signs of perinatal asphyxia, cardiorespiratory distress, or perinatal infection were observed. Infants with idiopathic apnea of prematurity were excluded. In some cases, antibiotic therapy was introduced for suspect but not proven bacterial infection and blue light applied

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for control of moderate jaundice. All babies were nursed in a thermally controlled environment and fed pooled breast milk. Milk intake was gradually increased so that calorie and fluid intake approximated 120 cal/kg and 180–200 ml/kg, respectively by the end of the 2nd wk.

Sodium supplementation was introduced on the 8th day in the form of 5% NaCl solution. For the less mature infants, higher sodium intake has been provided to cope with their greater urinary sodium loss and to ensure positive sodium balance. The required amount of NaCl was added to the breast milk and distributed in equal quantities throughout the day. Six of the 10 infants in group S had a birth weight less than 1500 g and received 5 mEq/kg/day NaCl. Infants with a birth weight of 1500–1750 g received 3 mEq/kg/day NaCl for a period of 2 wk. After this time, supplemental NaCl intake was halved for another period of 2 wk. NaCl supplementation was termined at the end of the 5th wk.

NaCl supplementation resulted in higher mean urinary sodium excretion and higher mean plasma sodium level in group S than in group NS infants. The infants gained weight at a similar rate irrespective of sodium intake (Table 1). The rate of growth was slightly greater, however, in the infants on NaCl supplementation than in those without.

For measurement of urinary hormone excretion, urine was fractionally collected for a period of 24 hr on the 7th day of life and at weekly intervals thereafter up to the 5th postnatal wk.

NA, DA, and 5-HT were measured in the same urine samples using a spectrofluorimetric method after aluminum oxide adsorption as modified by Hahn (14) using a Hitachi fluorimeter.

Student's t test was used for statistical analysis.

RESULTS

Figure 1 shows that urinary NA excretion in the NS group increased significantly from the initial value of 8.6 ± 1.5 μg/day to its maximum of 21.4 ± 5.5 μg/day ($p < 0.05$) in the 2nd wk followed by a gradual decline thereafter. When supplemental sodium was given, urinary NA excretion showed no consistent change, although a slight tendency to decrease could be seen. In weeks 2–3, the difference in urinary NA excretion between the two groups was significant ($p < 0.05$).

As shown in Figure 2, the trend and time course of urinary DA excretion were quite similar to that of NA. The mean value of 15.8 ± 2.4 μg/day in the 1st wk in group NS increased significantly to a peak value of 33.4 ± 6.0 μg/day in the 3rd wk ($p < 0.01$). Later a moderate fall occurred, but the mean value remained markedly elevated even at the end of the study. In contrast, the high dietary NaCl intake prevented any rise in urinary DA excretion in group S; mean DA excretion remained at about the same level during the whole period of study. DA excretion in weeks 2–4 proved to be significantly lower in group S than in group NS.

Figure 3 demonstrates that 5-HT excretion did not rise significantly above the initial value. Mean 5-HT excretion approximated 60 μg/day and showed no consistent change during the course of the study. Moreover, postnatal 5-HT excretion remained unaffected by NaCl supplementation.

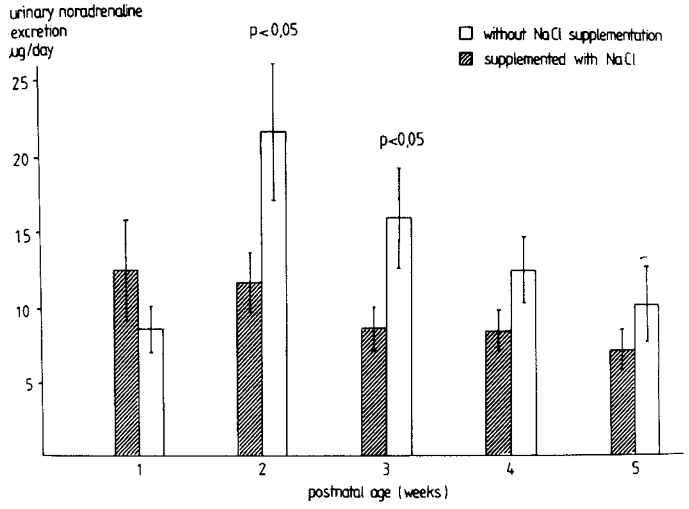

Fig. 1. Postnatal development of urinary noradrenaline excretion in premature infants with or without NaCl supplementation. *Bars*, mean ± SE.

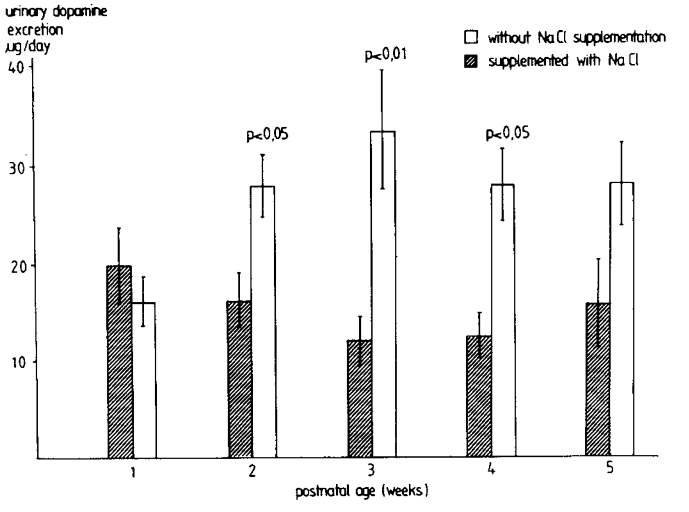

Fig. 2. Postnatal development of urinary dopamine excretion in premature infants with or without NaCl supplementation.

DISCUSSION

Using urinary CA excretion as an index of the activity of the sympathoadrenal system, a progressive increase in sympathoadrenal activity has been demonstrated with age in the newborn

Table 1. *The effect of NaCl supplementation on urinary sodium excretion, plasma sodium level, and weight gain in premature infants*

Age (wk)	Urinary Na execretion (mEq/kg/day)		Plasma Na level (mEq/liter)		Weight gain (g/kg/day)	
	Group NS	Group S	Group NS	Group S	Group NS	Group S
1	2.6 ± 0.6	2.9 ± 0.5	137.2 ± 3.1	136.6 ± 3.2	−8.0 ± 3.8	−9.1 ± 4.1
2	2.0 ± 0.5*	3.9 ± 0.7*	132.0 ± 2.5	135 ± 3.4	7.2 ± 2.6	11.2 ± 2.7
3	1.6 ± 0.5*	3.3 ± 0.7*	131.0 ± 2.4†	136.1 ± 1.8†	13.6 ± 1.8	16.3 ± 2.1
4.	1.0 ± 0.3†	2.2 ± 0.6†	130.5 ± 2.1*	136.9 ± 2.2*	15.8 ± 2.9	19.0 ± 2.3
5.	1.3 ± 0.5	2.3 ± 0.7	134.7 ± 2.8	137.6 ± 2.8	16.3 ± 2.5	21.5 ± 2.1

* $p < 0.05$.
† $p < 0.01$.

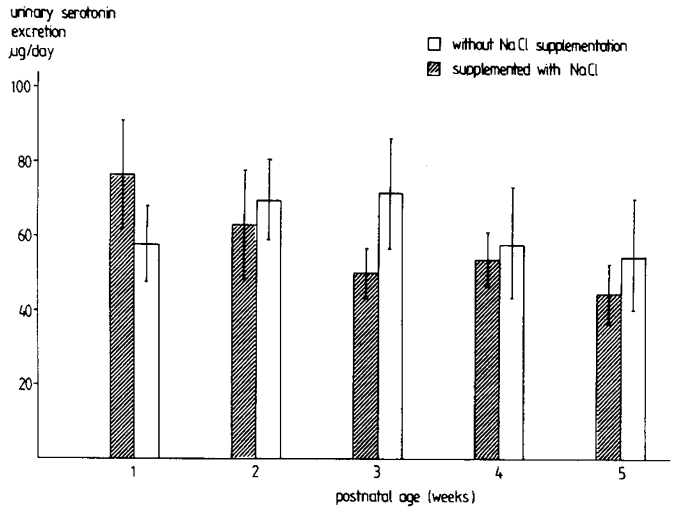

Fig. 3. Postnatal development of urinary serotonin excretion in premature infants with or without NaCl supplementation.

period and this maturation has been shown to correlate with the infant's condition (9, 19, 36). Namely, newborn infants subjected to cold environment or recovering from perinatal asphyxia had markedly increased NA, adrenaline, and DA excretion. Also, in newborn infants with respiratory distress syndrome, the urinary adrenaline and NA excretion ran parallel with the the clinical course (18, 19, 28, 30).

Our present findings support the view that sodium depletion enhances the activity of the renal sympathetic nervous system (2, 22, 25) even in low birth weight premature infants. In this regard, it is to be considered that, in addition to neural release, urinary CAs may be derived from glomerular filtration and tubular secretion (4). In the newborn period, no studies have been performed to quantitate the contribution of renal nerves and circulating CAs to urinary CA excretion or to estimate how salt intake may influence urinary CA excretion.

Furthermore, to our knowledge, no studies have been reported in human neonates to relate renal CA excretion to alterations in sodium balance. It is of interest, however, that Nicolopoulos *et al.* (20) observed a marked increase of VMA excretion, from 200 µg/day on the 1st day to 2600 µg/day on the 15th day in a group of healthy premature infants with birth weight of 1.8 ± 0.3 kg, whereas a slight decrease occurred in VMA excretion of full term neonates (from 600 to 480 µg/day during the same period). Moreover, a similar but less pronounced trend was found in urinary metacatecholamine excretion (20). Most recently, Bhat *et al.* (6) reported that urinary excretion of VMA, homovanillic acid, and 3-methoxy-4-hydroxyphenylglycol, the major metabolites of DA and NA, nearly doubled by 10–15 days in low birth weight premature infants; and in a mass fragmentographic study by Gabriel *et al.* (13), significantly higher plasma homovanillic acid and VMA levels were measured in preterm than full term neonates in the periods between 4 and 5 and 19 and 28 days after birth.

In the light of our present results, these findings can be interpreted as providing indirect evidence that the postnatal increase of urinary excretion and the sustained high plasma levels of CAs in low birth weight neonates might be due to urinary sodium loss and subsequent late hyponatremia rather than delayed maturation of enzyme systems involved in CA metabolism, as previously suggested (20, 21).

The clear association of sodium depletion with increased DA excretion and the reduction in DA excretion with restoration of sodium balance in the present study are at variance with the generally accepted natriuretic role of DA and seems to support the idea that DA, like NA, may enhance rather than inhibit renal tubular sodium reabsorption in premature infants. Similarly, low sodium intake in normal subjects resulted in an increase of plasma DA (25).

By contrast, Tulassay *et al.* (35) observed that in a group of sick premature infants presenting with severe cardiopulmonary distress administration of DA in a dose of 0.5–2.0 µg/min/kg produced an increase of sodium and water diuresis. Also, Pelayo and Jose (24) reported an age-dependent increase in DA-induced natriuresis in puppies, *i.e.* the renal response being less in the younger animals (24).

The apparent conflict of these data is hard to reconcile. One can speculate, however, that the physiological role of DA in the control of neonatal sodium metabolism differs from that seen later in life and the natriuresis induced by exogenous DA in the newborn period might be regarded as a pharmacological action of DA. It is of further concern that urinary DA excretion may increase in sodium-depleted premature infants independent of its regulatory role, since sodium depletion in itself can serve as a stressful stimulus.

The mechanisms by which renal CAs influence renal sodium conservation are not clear. Renal CAs may act to increase the activity of RAAS and to influence renal hemodynamics leading to a decrease in renal plasma flow and glomerular filtration rate (29). This latter possibility has not been tested since the postnatal course of renal blood flow and glomerular filtration rate has not been compared in the two groups.

As to the relationship between the function of RAAS and urinary CA excretion, the present results and our recently published data (34) clearly show that a parallel rise occurs in the activity of RAAS and in the urinary excretion of CAs in sodium-depleted premature infants; moreover, this rise can be prevented by NaCl supplementation. This observation supports the view that the function of these two endocrine systems may be related. In addition to a direct tubular effect to enhance sodium reabsorption, CAs also may stimulate the RAAS, while the high renin state in these infants may potentiate adrenergic release (37).

The present results also revealed that alterations in sodium balance did not induce alterations in the postnatal course of urinary 5-HT excretion, suggesting that 5-HT has no apparent influence on renal sodium handling during this early period of life. One might have expected on the basis of earlier data that 5-HT would reduce sodium excretion either directly (17) or indirectly through altering renal hemodynamics or increasing the activity of RAAS (15, 23, 38). However, this was not the case.

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Radioimmunoassay for Type I Procollagen in Growth Hormone-deficient Children before and during Treatment with Growth Hormone

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ABSTRACT. Type I procollagen concentrations were measured by radioimmunoassay in sera from 14 growth hormone-deficient children before and during 12 months of treatment with human growth hormone. Basal procollagen levels were lower than those of control children and comparable to those of normal adults. With treatment, the mean procollagen level increased into the range of the control children and was significantly greater than the baseline level at 1, 2, 3*, and 12 months ($p < 0.01$; $^*p < 0.05$). Although there was no significant statistical correlation between the growth velocity during treatment and the serum procollagen level, there was a suggestion that a high basal procollagen may be predictive of a less than optimal response to human growth hormone. (*Pediatr Res* 19: 8–11, 1984)

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Abbreviations

RIA, radioimmunoassay
hGH, human growth hormone
ANOVA, analysis of variance

Somatic growth results from the generation of new supporting and connective tissues. Since collagen is the major protein con-