Pediatr Nephrol (1993) 7: 871–875

Pediatric Nephrology

Review article

The influence of sodium on growth in infancy

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Received November 3, 1992; received in revised form January 16, 1993; accepted March 3, 1993

Abstract. Sodium (Na) is an important growth factor, stimulating cell proliferation and protein synthesis and increasing cell mass. Sodium chloride (NaCl) deprivation inhibits growth, as reflected by reduced body and brain weight, length, muscle and brain protein and RNA content and brain lipid content compared with controls. This is not due to deficiency of other nutrients since control and experimental diets were identical except for NaCl content. Subsequent NaCl supplementation restores growth velocity to control values but does not induce "catch-up" growth. In humans, salt loss causes growth failure and subsequent salt repletion improves growth. Preterm infants <32 weeks' gestation at birth are renal salt losers in the first 2 weeks of post-natal life and are vulnerable to hyponatraemia. This can be prevented by increasing Na intake, which also produces accelerated weight gain that persists beyond the period of supplementation. Early nutrition in preterm infants can affect subsequent growth and also cognitive function: this is probably multifactorial, but NaCl intake differed substantially between study groups and is likely to be an important factor. The mechanism whereby Na promotes cell growth is not understood, but stimulation of the membrane Na^+,H^+-antiporter with alkalinization of the cell interior is a likely possibility.

Key words: Sodium – Salt – Growth – Antiporter – Infant nutrition

Introduction

The total body content of sodium (Na^+) and chloride (Cl^-) is the major determinant of extracellular fluid (ECF) volume. This is so because changes in NaCl content are accompanied by parallel changes in water content, mediated by the hypothalamo-pituitary osmoregulatory system acting through thirst and vasopressin. An abrupt increase in Na^+ intake is followed by a rise in Na^+ excretion until a new steady state is reached, in which intake and output are again in balance. The change in Na^+ excretion is progressive rather than instantaneous, typically taking 3–4 days to complete. During this period of adjustment, ECF expansion occurs, most readily perceived as weight gain. Across a range of Na^+ intake from minimal to the maximum tolerated there is an approximately linear correlation between Na^+ intake and ECF volume. In the short term, therefore, increasing salt intake leads to weight gain: this might simplistically be interpreted as a growth-promoting effect. However, reducing salt intake to its original level leads promptly to loss of the retained ECF and a return to the original weight: true growth, meaning increased cell mass, has not taken place. Given that salt is the principal ECF solute, and that it exists only at low concentrations in intracellular fluid, a role for it in the process of cellular growth and replication is not intuitively obvious. However, there is both clinical and experimental support for such a role, and the weight of the evidence suggests that it is an important one and that it is necessary for normal growth and development of bone and nervous tissue, as well as for muscle protein synthesis.

Experimental studies

Fifty-five years ago Kahlenberg et al. [1] fed young rats a Na^+-deficient diet and showed that it was associated not only with impaired weight gain (Fig. 1) but also with diminished nitrogen retention. The rats were pair fed and the diets were equivalent in all nutrients other than Na^+, including Cl^-, suggesting that in these experiments Na^+ deficiency was specifically associated with the observed growth deficiency. More recently Aviv et al. [2] studied in detail the effect on rats of a period of Na^+ deprivation during the period of rapid growth (3–7 weeks' post-natal age), followed by a period of Na^+ supplementation during weeks 8 and 9. The study was partly designed to investigate the renal and hormonal responses to restoration of Na^+ intake, but also documented very clearly the adverse effects on growth of the Na^+ deprivation itself. The effects of

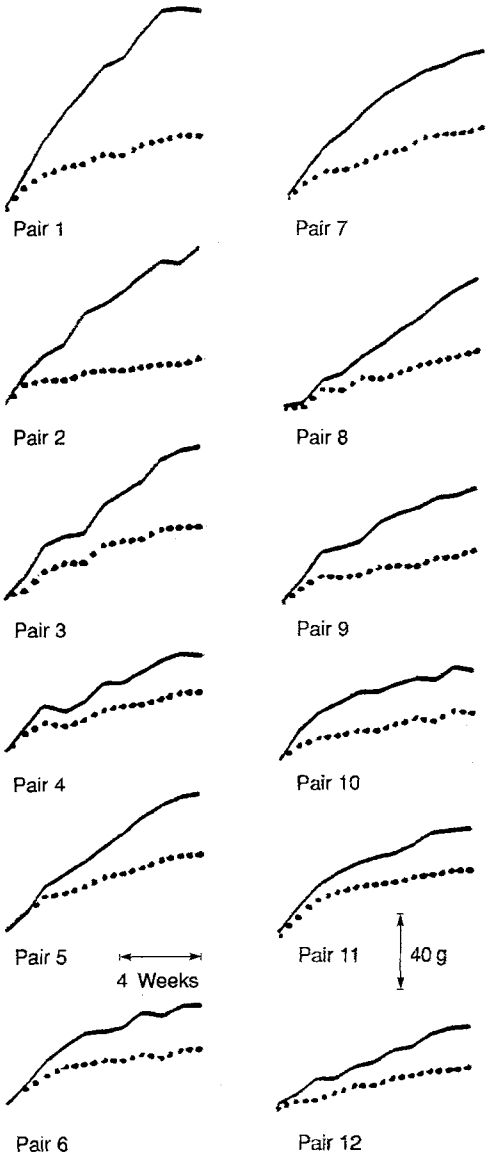

Fig. 1. The growth of albino rats over 10 weeks with (———) and without (– – – –) sodium (Na^+) in the diet; from ref [1] with permission

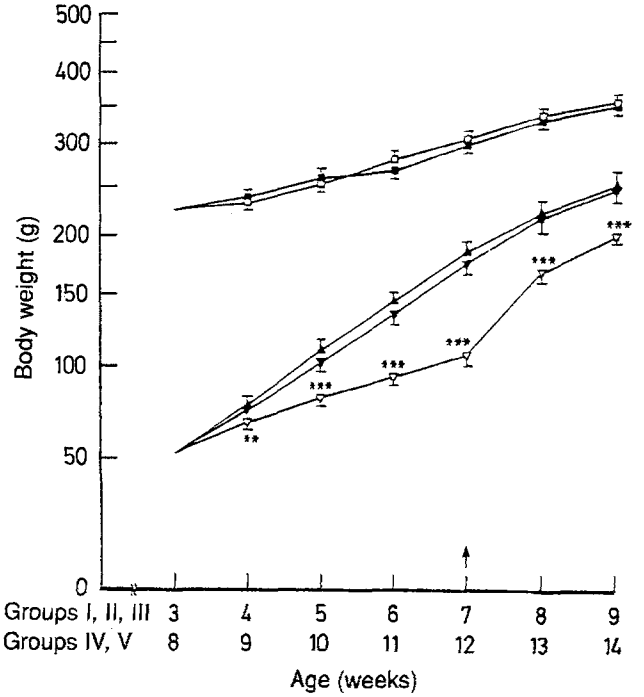

Fig. 2. Effects of different amounts of Na^+ on body weight as a function of age. * P <0.01 compared with group I; ** P<0.001 compared with group I; ▲, group I; ▼ group II; ▽, group III; □, group IV; ■, group V; ↑, transition from first to second phase. From ref [2] with permission

three different Na^+ intakes were studied: 8.9 mmol/kg per day (group I), 3.1 mmol/kg per day (group II) and 1.5 mmol/kg per day (group III). The two lower Na^+ intake diets were also administered to adult rats (8–14 weeks of age – groups IV and V). By comparison with groups I and II, group III rats were severely growth retarded. Provision of Na^+ supplementation produced immediate restoration of normal growth velocity to group III rats but, after an initial period of very rapid weight gain, they remained smaller than those in groups I and II (Fig. 2). In contrast, adult animals on the same Na^+ input as those in group III showed no adverse effects on growth. It is noteworthy that less than 50% of the weight gained by group III rats during the period of rapid weight gain following Na^+ supplementation was accounted for by expansion of the Na^+ space. This study suggests that: (1) Na^+ is necessary for normal growth in infant rats, (2) growth of the intracellular as well as the extracellular space requires Na^+ and (3) this effect is critically age dependent, maximally affecting animals during the most rapid period of post-natal growth.

Wassner [3] studied the effect of a Na^+-deficient diet on growth and muscle metabolism in weanling rats. All animals were fed a preparation containing 2–9 mmol Na^+/kg diet. Those in the experimental group (E) received distilled water to drink, while those in the control group (C) received distilled water containing 37 mmol/l NaCl. Growth was markedly impaired in E compared with C both in weight and length, despite the fact that total food intake over the 15-day study period was not different between groups. E animals were 31% lighter than C but ECF volume (inulin space) only differed by 4%. Protein synthesis, measured as the rate of phenylalanine incorporation into epitrochlearis muscle, was significantly lower in E than C, while protein breakdown, measured as the rate of tyrosine release with and without the presence of insulin, was the same in both groups. Epitrochlearis muscle weight in E was only 68% of that in C: the protein content per gram of muscle was the same in the two groups, but gastrocnemius RNA content in E rats was only 72% of the C value. These results strongly support the hypothesis that Na^+ deficiency impairs both height and weight gain and that the effect is at least in part due to impaired protein synthesis. More than 80% of muscle RNA is ribosomal and a reduction in its concentration is consistent with diminished protein synthetic capacity.

In a later study [4], Wassner went on to investigate the effect of restoring dietary Na^+ intake to weanling rats previously Na^+ depleted. Salt supplementation rapidly re-

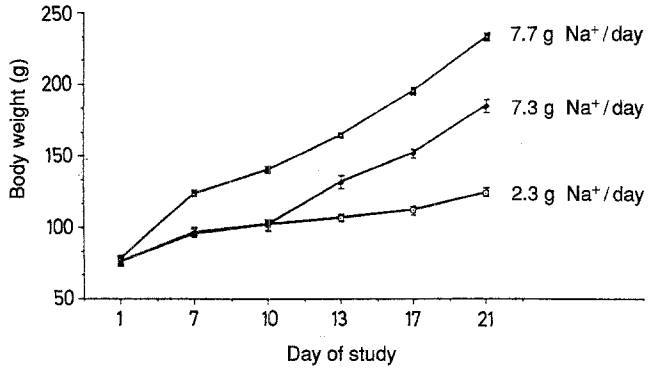

Fig. 3. Body weights of Na^+-deficient (□), Na^+-supplemented (◆) and control (■) rats. From ref [4] with permission

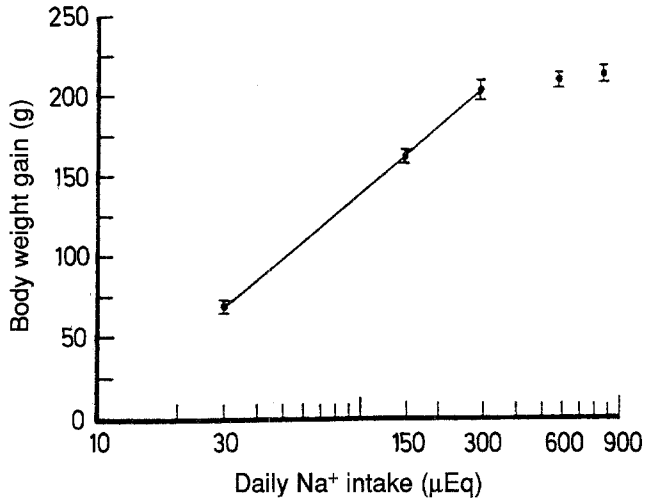

Fig. 4. Total weight gain as a function of daily Na^+ intake during the 5-week study. Doses of Na^+ higher than 300 μEq daily showed no further effect on growth. Mean ± SEM, $n = 8$, $y = -128+133$ log dose, $r = 0.96$, $P < 0.001$. From ref [5] with permission

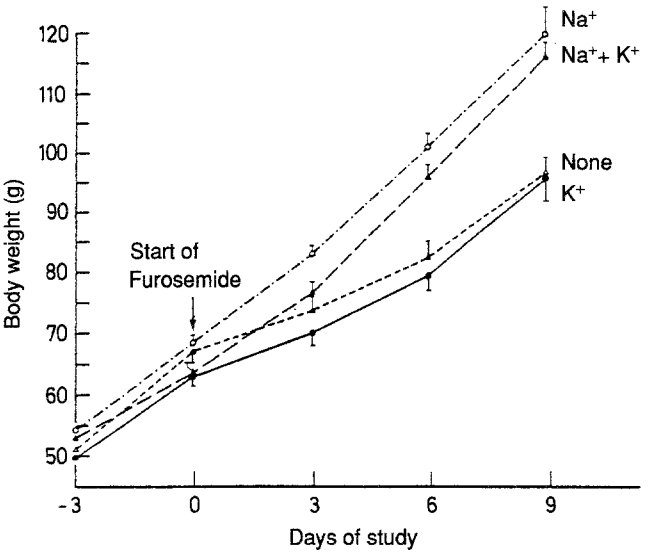

Fig. 5. Growth rates during administration of frusemide (100 mg/m²) with and without Na^+ and/or potassium (K^+) replacement. Points represent mean ± SE, $n = 8$. From ref [7] with permission

stored to normal the rate of increase of both height and weight (Fig. 3) and reversed the abnormalities of protein synthesis and muscle RNA described in the previously study. It is noteworthy that, despite normalization of growth velocity, "catch-up" growth was not observed; the Na^+-deficient rats remained smaller at all ages within the study period than control animals. Both liver and kidney weights were significantly lower in E than C animals. It should be mentioned that in both Wassner's studies the diet was deficient in Na^+ but not Cl^-, confirmed by the normal plasma Cl^- concentrations and the production of Na^+-free urine of high Cl^- concentration. It thus appears that Na^+ per se, not necessarily NaCl, is required for normal growth. This does not rule out an independent effect of Cl^- deficiency, but that issue is not addressed in most of these studies.

Fine et al. [5] investigated the effect of dietary Na^+ intake on growth and body composition in weanling rats. They found that normal growth required a Na^+ intake of 300 μmol daily, corresponding to 60 μmol Na^+/g of new growth. Below this intake there was a linear relationship between Na^+ intake and growth velocity, but supplementation above this amount had no additional growth-enhancing effect (Fig. 4). Total body nitrogen, reflecting protoplasmic growth, was likewise strongly related to Na^+ intake across the same range of values. Because Na^+-deprived animals ate less than Na^+-replete ones, a pair-feeding study was also performed. This showed that growth was still superior in animals given salt than in those deprived of it. In other words, the energy cost per gram of new tissue was greater in Na^+-deprived animals than in controls.

Chronic frusemide administration causes growth retardation and decreased bone mineralization in growing rats. One possible explanation of this, favoured by Koo et al. [6], is that frusemide causes increased urinary excretion of calcium (Ca^{2+}) and magnesium (Mg^{2+}), thus leading directly to skeletal demineralization. However, in a similar study Fine et al. [7] showed that the growth-inhibiting effect of frusemide was completely reversed by supplementation with Na^+ alone, or Na^+ plus K^+, but supplementation with K^+ alone had no effect (Fig. 5). Furthermore, adding Na^+ to the diet abolished the negative effect of frusemide on Ca^{2+} and Mg^{2+} balance. These findings strongly suggest that Na^+ depletion, rather than some other pharmacological effect of the drug, is responsible for the growth-inhibiting action of frusemide.

Bursey and Watson [8] studied the effect of feeding a salt-deficient diet to pregnant rats on brain development in their offspring. There were four groups (I-IV) given diets containing 0.173%, 0.067%, 0.040% and 0.022% Na^+ throughout gestation. They consumed respectively 1.56, 0.59, 0.26 and 0.17 mmol Na^+ daily. Mothers in the two lower intake groups (III and IV) gained less weight during pregnancy and had reduced litter size and early survival – none of the group IV infants survived 21 days' lactation. Maternal Na^+ intake correlated with brain weight (wet and dry), cholesterol content, protein: DNA ratio and RNA: DNA ratio in those that survived 21 days. Na^+ intake was not restricted during lactation. Although birth weight

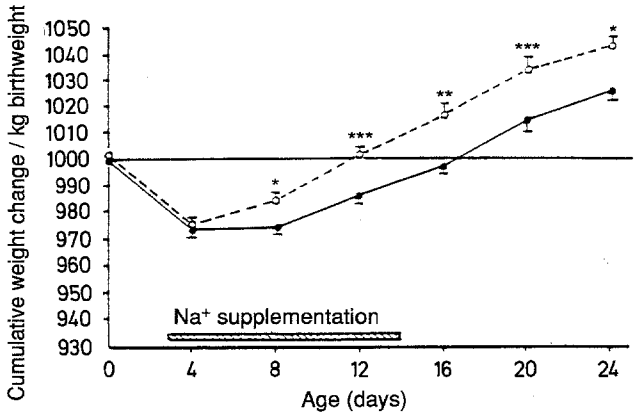

Fig. 6. Cumulative weight changes standardized for birthweight and plotted at 4-day intervals in Na^+-supplemented (group A, ○) and unsupplemented (group B, ●) infants; * $P < 0.01$, ** $P < 0.005$, *** $P < 0.001$. From ref [10] with permission

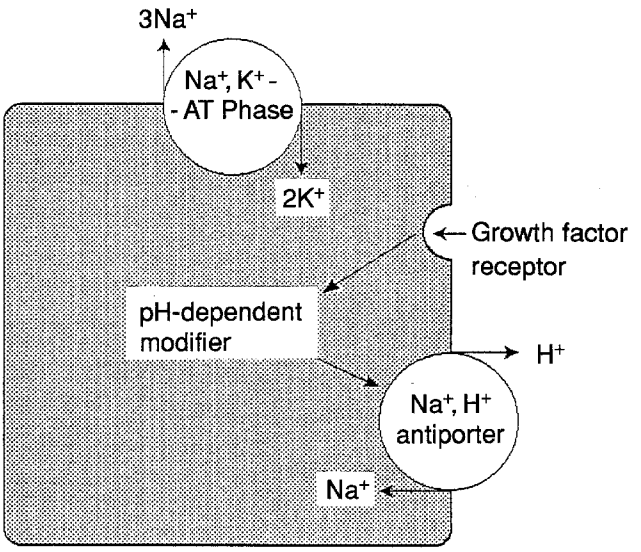

Fig. 7. Schematic representation of the antiporter and some of its probable relationships

was correlated with maternal Na^+ intake the difference had disappeared by 21 days. These results suggest a specific adverse effect of Na^+ deficiency during the intrauterine period on brain growth and development which may not be reversible by later Na^+ repletion. It may be relevant to mention that the last third of pregnancy in the rat corresponds roughly with the neonatal period in the human as regards organ growth and differentiation.

Clinical studies

Consistent data are naturally more difficult to obtain in the clinical setting than in the research laboratory. Nevertheless, published observations indicate that Na^+ is as necessary for tissue growth in human infants as it is in experimental animals. Bower et al. [9] studied 11 infants with ileostomies. All had substantial Na^+ and bicarbonate (HCO_3^-) losses in the ileostomy fluid leading to Na^+ depletion and metabolic acidosis. Urine Na^+ was <10 mmol/l in each infant in the absence of oral Na^+ supplementation, although plasma Na^+ was normal in all. Despite adequate energy and protein intake, 6 infants failed to grow. Satisfactory growth occurred in all 6 when additional Na^+ was given, whether given as NaCl (3 patients) or $NaHCO_3^-$ (3 patients). Normal growth occurred when urinary Na^+ concentration rose to >10 mmol/l in each case. In our own studies of infants born before 34 weeks' gestation [10], supplementation with NaCl to a total Na^+ intake of 4–5 mmol/kg per day from the 4th to the 14th post-natal day led to earlier onset of post-natal growth and improved weight gain throughout the period of supplementation compared with a control group who received 1–1.5 mmol/kg per day. The difference between supplemented and unsupplemented infants persisted beyond the period when extra salt was given, at least to the end of the 1st month (Fig. 6), suggesting that the additional weight gained by the supplemented babies was not accounted for solely by ECF volume expansion.

Several studies have examined the effect of different kinds of milk on growth and developmental outcome in premature babies. Gross [11] compared mature human milk (M) with milk expressed from mothers of premature infants (P) and with a whey-based formula (W) which also had higher mineral content than the mature human milk. Growth was significantly better in both P and W than in M, in weight, crown-heel length and head circumference. The feeds were isocaloric: P and W contained greater amounts of protein, Na^+, Cl^-, K^+, Ca^{2+} and phosphorus than M. It is not possible to state which of these differences is responsible for the difference in outcome, but the author noted that 50% of M babies became hyponatraemic compared with only 15% of P and 20% of W. It is certainly possible, and perhaps likely, that Na^+ contributed to the observed result. Identical results were obtained in very similar studies by Atkinson et al. [12], Brooke et al. [13] and Lucas et al. [14]. In a later paper Lucas et al. [15] reported a startlingly large benefit in developmental status at 18 months in babies who had been fed nutrient-enriched 'preterm' formula or their own mothers' milk compared with those fed standard 'term' formula. Here again, the results do not allow the conclusion that Na^+ was responsible for all the difference, but it is likely to have contributed. This is supported by the observation that, in a large follow-up study of very low birth weight babies, a history of neonatal hyponatraemia was a more consistent predictor of poor neurodevelopmental outcome than a history of hypoglycaemia, jaundice or any other variable examined (Brothwood M, personal communication).

Mechanism of growth-enhancing effect of Na^+

How might Na^+ support, and Na^+ deficiency inhibit, cell growth? A large and growing body of evidence implicates the Na^+-H^+ antiporter, present in many types of cell membranes, as an important mediator of cell growth and pro-

liferation by its action in alkalinizing the cell interior. The antiporter is a protein that binds one univalent cation on the outer side of the cell membrane and another on the inner side and exchanges them. It is energized by secondary active transport, i.e. in normal circumstances the large ECF-to-cell Na^+ gradient, established by the action of Na^+,K^+-ATPase in removing Na^+ from the cell against its gradient, causes extrusion of H^+ from the cell and a rise in intracellular pH. In experimental conditions, if the gradients are reversed transport occurs in the opposite direction. The antiporter also binds and transports lithium and ammonium and is blocked by amiloride. A rise in intracellular H^+ concentration (fall in pH) increases antiporter activity without altering the 1 : 1 stoichiometry: there appears to be an intracellular H^+-dependent modifier site, which is part of, or associated with, the antiporter (Fig. 7). Numerous growth factors stimulate antiporter activity, possibly by interacting with this modifier site. These include epidermal growth factor, platelet-derived growth factor, insulin, angiotensin, lys-bradykinin, vasopressin, thrombin, bombesin and interleukin 2 (some of these affect specific cell types only: for example, thrombin stimulates antiporter activity and proliferation in platelets, angiotensin II in vascular smooth muscle). Almost certainly, it is the rise in intracellular pH that is the main stimulus to cell growth and proliferation: alkalinization of the medium causes cell division even if the antiporter is blocked. Increased antiporter activity also stimulates Na^+,K^+-ATPase as a result of increased intracellular Na^+, leading to a rise in cell K^+ which is also necessary for growth.

Because of the bidirectional nature of the antiporter, anything that alters the transmembrane gradients for Na^+ or H^+ will increase or decrease transport. Reduced availability of Na^+ in the ECF will inhibit H^+ extrusion and cause intracellular pH to fall: ECF acidosis will have a similar effect. Thus Na^+ repletion enhances and Na^+ depletion inhibits antiporter activity, with predictable effects on intracellular pH and therefore cell growth and division. The role of the antiporter in cell growth is discussed in two recent reviews [16, 17]. It is entirely possible that other, antiporter-independent mechanisms contribute to the effect of Na on growth: different processes may be involved in different tissues.

Conclusion

Growth is a complex, multifactorial process that can be rate limited by many adverse factors, some of which are nutritional. Common sense dictates that each essential component of living tissue must be present in the diet in the necessary amount if cell replication is to occur. The evidence discussed in this paper, however, strongly supports the view that Na^+ is a growth factor exerting effects that go far beyond its minimal role as a constituent of new tissue.

'If the salt shall lose its savour, wherewith shall it be salted?'

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