Angiotensin converting enzyme activity in infancy is related to birth weight

J S Forsyth, J Reilly, C G Fraser, A D Struthers

Arch Dis Child Fetal Neonatal Ed 2004;89:F442-F444. doi: 10.1136/adc.2003.027896

Aims: (a) To measure infant angiotensin converting enzyme (ACE) activity in healthy term infants at birth and during the first three months of life. (b) To determine the relation between serum ACE activity and infant feeding practice during this period. (c) To investigate the relation between serum ACE activity and birth weight and other potential contributing factors including acid-base status at birth, gestation, and maternal ACE genotype.

Methods: Prospective study of term infants, with clinical and feeding data collected from parents and medical records, and serum ACE measured in the infant at birth and 1 and 3 months of age, and in the mother at the time of birth and one to three months after birth.

Results: At birth and 1 and 3 months of age, infant serum ACE activity was twice that of maternal ACE activity. Infant ACE activity at birth and 1 and 3 months did not significantly differ between breast and formula fed infants. There was a highly significant negative correlation between infant ACE activity at 3 months and birth weight (r = −0.52; p < 0.001). This persisted after the conversion of birth weights to z scores (r = −0.34; p = 0.03). ACE activity at 3 months was also related to placental weight (r = −0.30; p = 0.02) and maternal age (r = −0.30; p = 0.05). The strong correlation between serum ACE activity and birth weight z score persisted after adjustment for maternal age and placental weight (r = −0.34; p = 0.03).

Conclusion: As ACE is increasingly identified as a risk factor for cardiovascular disease, serum ACE activity in infancy may contribute to the link between low birth weight and later cardiovascular events.

T
here are numerous reports of low birth weight being associated with coronary heart disease, hypertension, stroke, and non-insulin dependent diabetes. These associations are thought to be the consequence of a stimulus or an insult occurring at a critical period of early life and resulting in permanent effects on structure and metabolism. There is evidence that this concept of “programming” may not be exclusive to intrauterine life, and nutritional interventions during the postnatal period may also influence later health. For example, recent data indicate that children who are breast fed in infancy have lower blood pressures during later childhood and adolescence than children who are formula fed. Although there are several constituents of breast milk that are possible causes, including hormones, nutrients, and trophic substances, the underlying mechanisms remain uncertain.

Angiotensin converting enzyme (ACE) not only has a key role in the regulation of peripheral blood pressure, but it is now increasingly being identified as a major risk factor for cardiovascular disease. There is some evidence that ACE activity may be increased in preterm infants especially those with respiratory distress syndrome in the newborn period. Infant lung capillaries are a rich source of ACE, and hypoxic mice are known to have raised serum ACE activity at birth. Whether this increased activity is related to lung immaturity or to other associated factors, including hypoxia and intrauterine growth, has not been determined. Moreover, it is not known whether raised ACE activities are sustained beyond the immediate newborn period.

There are no published data relating ACE activity to infant feeding practice. However, there is evidence that milk contains peptides that inhibit serum ACE activity. The inhibitory effect of these peptides on ACE activity may be more obvious in breast fed infants as whey proteins have a strong inhibitory effect and these predominate in breast milk. Moreover, the intestinal flora of breast fed infants is dominated by bifidobacteria that traditionally ferment milk proteins into ACE inhibitory peptides.

The aims of this study were therefore to (a) measure infant serum ACE activity in healthy term infants at birth and during the first 3 months of life, (b) determine the relation between serum ACE activity and infant feeding practice during this period, and (c) investigate the relation between serum ACE activity and birth weight and other potential contributing factors including acid-base status at birth, gestation, and maternal ACE genotype.

METHODS

The infants were recruited to the study during the early postnatal period, after informed consent had been obtained from their mother or guardian. They were born at term (259-294 days) and had already received their first breast or formula feed.

Clinical data were collected prospectively. These included placenta weight, gestation, mode of delivery, and birth weight. Infant feeding information included type of milk feed at birth and number of breast, formula, and solid feeds at 1 and 3 months of age. Maternal blood pressure was measured one to three months after delivery.

Umbilical cord blood was obtained immediately after birth to measure acid-base status and serum ACE activity. Capillary samples (100 µl) were taken from the infant at 1 and 3 months of age to measure serum ACE activity. A venous blood sample was taken from the mother to determine ACE genotype and also to measure maternal ACE activity at birth and one to three months after delivery.

Serum ACE activity was measured by an automated technique that requires small volumes of blood (100 µl). ACE was assayed by monitoring the change in absorbance at 340 nm caused by the hydrolysis of furylacryloyl-phenylalan-nylglycylglycine to furylacryloyl-phenylalanine and glycyglycl- cine (Sigma Aldrich Chemical Co, Poole, Dorset, UK) on an
Angiotensin converting enzyme activity and birth weight

Maternal and infant genotype (II, ID, DD) (significantly. Maternal ACE activity correlated positively with activity. Maternal ACE activity measured at the time of birth and 3 months. At birth and 1–3 months, infant was also significantly more variance at 1 month of age than age but both were significantly higher than at birth. There were no significant differences the serum ACE activity in infants at birth and 1 and 3 months of age. There were exclusively breast fed at 3 months. However, only 22% of infants data were therefore not confounded by factors that had

RESULTS

Sixty eight infants were recruited to the study. Table 1 shows the maternal and infant characteristics. No infant had a positive history of maternal hypertension, and there were no major neonatal problems. All infants started milk feeds within four hours of birth. Table 2 shows feeding details.

Table 2 Feeding characteristics

<table>
<thead>
<tr>
<th>Feed at birth</th>
<th>No of feeds/day at 1 month</th>
<th>No of feeds/day at 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>5.4 (4.6)</td>
<td>3.0 (3.7)</td>
</tr>
<tr>
<td>Formula</td>
<td>0.0 (0.0)</td>
<td>6.7 (1.3)</td>
</tr>
<tr>
<td>Breast</td>
<td>5.4 (3.6)</td>
<td>3.5 (3.0)</td>
</tr>
<tr>
<td>Formula</td>
<td>0.0 (0.0)</td>
<td>5.3 (1.1)</td>
</tr>
</tbody>
</table>

Values are mean (SD).

Table 3 Maternal and infant angiotensin converting enzyme (ACE) activity (units/l)

<table>
<thead>
<tr>
<th>ACE activity</th>
<th>N</th>
<th>ACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth</td>
<td>67</td>
<td>29.5 (12.2)*</td>
</tr>
<tr>
<td>1–3 months</td>
<td>43</td>
<td>33.6 (12.5)†</td>
</tr>
<tr>
<td>Infant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth</td>
<td>67</td>
<td>56.0 (23.2)†</td>
</tr>
<tr>
<td>1 month</td>
<td>52</td>
<td>78.3 (40.2)†</td>
</tr>
<tr>
<td>3 months</td>
<td>42</td>
<td>72.8 (22.8)*</td>
</tr>
</tbody>
</table>

Values are mean (SD).

Table 4 Relation between feeding practice and infant angiotensin converting enzyme (ACE) activity (units/l)

<table>
<thead>
<tr>
<th>Predominant feed</th>
<th>ACE activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominant feed</td>
<td>Birth</td>
</tr>
<tr>
<td>Breast milk</td>
<td>55.0 (15)*</td>
</tr>
<tr>
<td>(n = 31)</td>
<td></td>
</tr>
<tr>
<td>Formula</td>
<td>57.6 (23)*</td>
</tr>
<tr>
<td>(n = 21)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD).

DISCUSSION

This study of healthy term infants shows that infant serum ACE activity at 3 months of age is related to size at birth but not to breast or formula feeding. A possible implication of these findings is that components of the renin-angiotensin pathway may be directly or indirectly linked to mechanisms that influence fetal growth.

Previous human data on ACE activity have been linked to specific pathological circumstances including maternal hypertension, prematurity, and infant respiratory and acid-base abnormalities. Moreover, measurements of serum ACE activity have been limited to the immediate newborn period. There are no published longitudinal data on healthy term infants and the relation of serum ACE activity to type of infant feeding. Recruits to this study were born at term after a normal pregnancy, they had normal acid-base status at birth, and there was no history of maternal hypertension. The data were therefore not confounded by factors that had

serum ACE activity at 3 months and birth weight z score persisted after adjustment for maternal age and placental weight ($r = -0.34; p = 0.03$).
previously been reported to be associated with raised infant serum ACE activity. Despite this relatively homogeneous study population, a significant correlation between birth weight and infant serum ACE concentration at 3 months of age was noted.

Previous studies have reported higher serum ACE activity in infants than adults. It is known that lung endothelial cells are a rich source of circulating ACE and therefore the raised activities in infants may be related to rapid lung development that occurs during the last trimester and the immediate postpartum period. Several studies have indicated that serum ACE activities are higher in preterm infants, suggesting that ACE may be more active in the immature lung.

The variance in ACE activity at 3 months of age was significantly less than that at birth and 1 month. Serum ACE activity at birth and 1 month of age was not related to weight at birth, but there was a highly significant negative correlation between infant ACE activity at 3 months and birth weight. This correlation persisted when the birth weights were converted into z scores. In this cohort of term infants, gestation was not independently related to ACE activity. The serum ACE activities at 3 months were therefore not only more stable, but they also related significantly to variation in birth weights within a narrow gestational range.

This strong association between birth weight and serum ACE suggests that ACE or the renin-aldosterone system may play a specific growth factor-like effect on target tissue, and it has been proposed that the renin-angiotensin system has a pivotal role in fetal development and growth. There is laboratory evidence indicating that angiotensin II has a specific growth factor-like effect on target tissue, and it is known that lung endothelial cells are a rich source of circulating ACE.

Authors’ affiliations
J S Forsyth, J Reilly, Tayside Institute for Child Health, University of Dundee, Scotland, UK
C G Fraser, Biochemical Medicine, University of Dundee
A D Struthers, Clinical Pharmacology and Therapeutics, University of Dundee

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doi: 10.1136/adc.2003.027896

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