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Increased Activity of the Renin-Angiotènsin-Aldosterone System During the Perinatal Period

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Plasma renin activity (PRA), plasma renin substrate (PRS), plasma renin concentration (PRC), and plasma aldosterone concentration (PAC) were measured in normal full-term newborn infants and infants up to 22 days after birth (36 in all). As compared to the control, PRA and PAC levels were significantly higher ($p < 0.001$) in cord blood, and in 2 to 6 and 12 to 22 day old infants. The high values of PRA in 2 to 6 day old infants were due to the high PRS values. In cord blood and in 12 to 22 day old infants, however, the high levels of PRA reflect elevation of PRC.

No correlation was found between PRA, PAC and serum potassium in cord blood and in 2 to 6 day old infants, but there was a significant correlation between the parameters ($r = 0.72$ and $p < 0.02$) in 12 to 22 day old infants, indicating that at this age, as in healthy adults, the renin-angiotensin system and serum potassium seem to be the major stimuli for aldosterone secretion.

It has been reported previously that the neonatal period is characterized by high levels of plasma renin activity (PRA) and plasma aldosterone concentration (PAC) (5, 6, 9, 10, 15, 16). It is not clear, however, if these are due to an increase in plasma renin concentration (PRC) or to a rise in plasma substrate concentration (PRS).

There have been few studies of PRC and PRS patterns in foetus at term (6, 8, 9, 19) and newborn children during the first weeks of life (8, 10) in part at least because of the large quantities of blood required for measuring the different components of the system.

We undertook the present study in order to obtain further information of PRS, PRC and PAC patterns during the perinatal period, following a kinetic method previously published by us (3).

Materials and Methods

The subjects were 36 normal full term newborn infants, up to 22 days old, with

a mean birth weight of 3059 g and Apgar score at 1 min of 8-9. Mothers were on a normal sodium intake during pregnancy and newborn infants did not suffer from any internal disease and did not receive any medication which might have influenced the renin-angiotensin system. The infants received a diet containing 19.5 mg/100 ml Na and were divided in three groups:

Group 1. Eleven normal term foetuses. Blood samples were obtained from umbilical cord venous blood at the time of delivery.

Group 2. Fifteen newborn infants aged from 2 to 6 days.

Group 3. Ten newborn infants aged from 12 to 22 days.

Control: Eighteen healthy adults aged 21 to 30 years.

Peripheral venous samples were obtained in group 2 and 3 in the recumbent position between 09.00 and 11.00 a.m. The samples were analyzed for PRA, PRS, PRC, PAC, sodium, and potassium.

PRA (as angiotensin I generated, in ng/ml/h) and PAC, were measured by radioimmunoassay method (7, 18).

PRS and PRC were measured by a kinetic method described previously (3). The maximal angiotensin I (A I) generated during incubation (A I generated as $t \rightarrow \infty$) was used to evaluate the PRS. It was obtained plotting the reciprocal value of A I generated against the reciprocal of correlated incubation times. PRS was expressed as ng/ml A I.

The specific velocity constant of reaction (K) was used to deduce the PRC, derived from the expression:

$$K = \frac{1}{t} \ln \frac{S_o}{S_o - P}$$

S_o is the initial renin-substrate concentration, and P is the A I generated at time t. PRC was expressed as $h^{-1} \times 10^{-3}$.

Sodium and potassium serum concentrations were determined by flame photometry.

The normal value in healthy adults for all these parameters have been previously published (1).

Statistics. All the results in the text and figures are reported as mean ± SEM. Statistical analysis were performed by using the Student test for paired values and the p levels are indicated in the figures.

Results

The PRA levels in cord blood and in 2 to 6 and 12 to 22 day old infants were 11.45 ± 1.72, 24.7 ± 2.84 and 8.73 ± 0.95 ng/ml/h, respectively. These values were all significantly higher than normal adult values of 1.61 ± 0.2 ng/ml/h (fig. 1). In 2 to 6 day old infants the mean PRA was higher than in the other groups.

PRS also was markedly elevated above the normal range (20.57 ± 4.17 ng/ml) in group 2 (514.70 ± 69.7 ng/ml), but only slightly elevated in cord blood (49.25 ± 6.55 ng/ml) and in the 12 to 22 day old group (38.0 ± 4.06 ng/ml) (fig. 1).

As shown in figure 1, PRC was also higher in cord blood (283 ± 29 $h^{-1} \times 10^{-3}$) and in the 12 to 22 day old group (255.7 ± 18.34 $h^{-1} \times 10^{-3}$) than in normal adults (72.0 ± 3.84 $h^{-1} \times 10^{-3}$). In group 2, PRC was slightly lower (52.8 ± 6.33 $h^{-1} \times \times 10^{-3}$) than in healthy adults.

PAC in groups 1, 2 and 3 were 376.0 ± 77.6 pg/ml, 749.2 ± 68.4 pg/ml and 617.5 ± 98.8 pg/ml, respectively. These values were all significantly higher than in normal adult values of 46.07 ± 7.05 pg/ml (fig. 2).

A significant correlation was found between PRA and PRC ($r = 0.61$, $p < 0.05$) in group 3. When PAC values were plotted against serum potassium, no correlation was found ($r = 0.25$). Comparing the addition of PRA and serum potassium con-

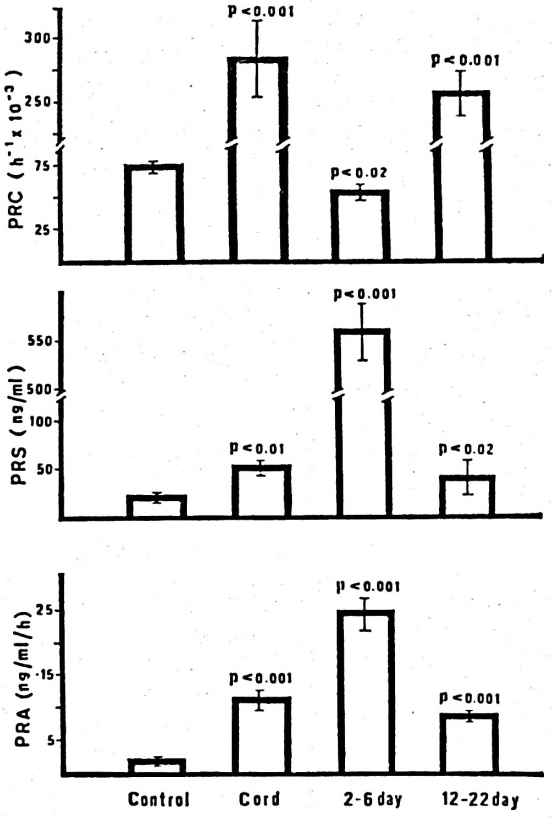

Fig. 1. *Comparison of mean values ± S.E. of plasma renin activity (PRA), plasma renin substrate (PRS) and plasma renin concentration (PRC) in control subjects (n = 18), cord blood (n = 11) and infants aged 2-6 days (n = 15) and 12-22 days (n = 10).*

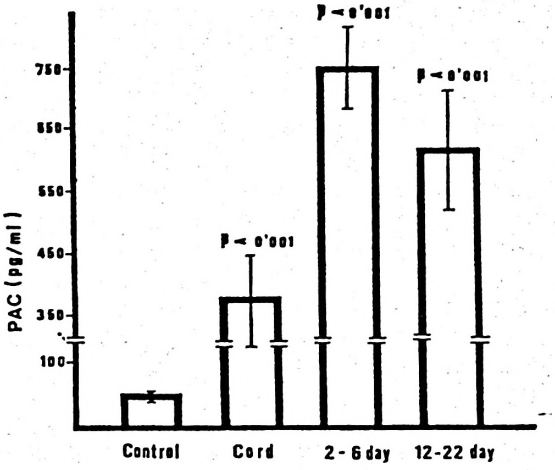

Fig. 2. *Comparison of mean values ± S.E. of plasma aldosterona concentration (PAC) in control subjects (n = 18), cord blood (n = 11) and infants aged 2-6 days (n = 15) and 12-22 days (n = 10).*

centrations with PAC, however, revealed a better significant correlation in group 3 ($r = 0.72$, $p < 0.02$).

On the other hand, we found no correlation between PRA and PAC in group 1 ($r = -0.38$) and group 2 ($r = 0.44$). Moreover, there was no significant correlation between PAC values and serum potassium concentration in these age groups.

Finally, comparing the addition of PRA and serum potassium concentration with PAC revealed no correlation in groups 1 and 2.

Discussion

The elevated PRA found in cord blood (considered as reflecting the blood of foetus at term) and in infants, 2 to 6 days and 12 to 22 days, confirm the results of other studies (5, 6, 10, 13, 15, 16). PRA was essentially of the same magnitude (5-7 times above the control value) in foetal blood as in that of infants 12 to 22 days, but PRA was higher (15 times above the control value) in that of infants 2 to 6 days. Several authors (5, 10, 13) found that PRA tends to increase in the first days of life and during 6 days after birth. PRA is dependent upon substrate as well as enzyme concentration because the reaction between renin and renin substrate to form angiotensin follows first order kinetics (3, 11). Inded, using a kinetic method without added exogenous renin or renin substrate (3), our data in-

dicate that the increase PRA in cord blood and in newborn infants 12 to 22 days old reflect elevation of PRC. The elevated substrate levels in the infants in the first days of life have previously been reported by KOTCHEN *et al.* (10) in 1972. This elevation has been attributed to an oestrogen effect on protein synthesis in the infant during the perinatal period. Our results, however, do not agree with those of HAYDUK *et al.* (8) and GODAR *et al.* (6) who detected an increase in PRC in the fist days of life, while the substrate remained between normal range. These discrepancies may be explained by differences in methodology.

The present results regarding PRC and PRS in cord blood and in 12 to 22 day old infants are consistent with the observations of other investigators (9, 19), who have found that PRC increased in the neonatal period while PRS levels stayed on normal range or slightly increased.

The results of this study as of others (6, 9, 10), clearly demostrate increased activity of the renin-angiotensin system in the perinatal period, suggesting that the kidney and liver of the foetus and newborn infant are able to respond to the same stimuli as the kidney and the liver of healthy adults.

PAC has been found to be elevated in cord blood during the first week of life (2, 5, 6, 9, 12, 14, 15) and in older newborn infants (4, 5, 14, 17). The high levels may be due to the renin-angiotensin system, serum potassium and ACTH, which are known to be involved in the regulation of aldosterone production and secretion.

No correlation between PRA, potassium and PAC in either cord or infants at 2 to 6 days after birth has been found, in agreement with the observations of KATZ *et al.* (9) and SIEGLER *et al.* (14).

This does not exclude the participation of these factors in the regulation of aldosterone secretion during the perinatal period. It may reflect the rapid changes in plasma volume and electrolyte balance that characterize the early days of life (14).

In 12 to 22 day old infants PRA was correlated significantly with PAC and this correlation was better when PAC were plotted against PRA and serum potassium at the same time. This indicates that in the conditions of this study and at this age of life, the renin angiotensin system and serum potassium seem to be the major stimuli of aldosterone secretion.

Resumen

Se determinan en recién nacidos a término y en niños en los primeros 22 días de vida (36 casos en total), los niveles de actividad plasmática de renina (APR) y concentración plasmática de substrato (CPS), de renina (CPR) y de aldosterona (CPA). Los niveles de APR y CPA fueron significativamente más altos ($p < 0,001$) en sangre de cordón y en los grupos de 2 a 6 días y de 12 a 22 días de vida que en el grupo control. Estos elevados valores de APR en el grupo de 2 a 6 días parece deberse a unos niveles elevados de CPS. En la sangre de cordón y en el grupo de 12 a 22 días, sin embargo, los niveles de APR reflejan una elevación de CPR.

No se ha encontrado ninguna correlación entre APR, CPA y potasio en cordón ni en el grupo de 2 a 6 días, existiendo, sin embargo, una correlación significativa entre esos parámetros en el grupo de 12 a 22 días ($r = 0,72$; $p < 0,02$), lo que indica que a esta edad, como en los adultos sanos, el sistema renina-angiotensina y el potasio parecen ser los estímulos más importantes para la secreción de aldosterona.

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