

Selective increases in adrenal steroidogenic capacity during acute respiratory disease in infants

Aaron Hanukoglu, Daniel Fried, Ishak Nakash and Israel Hanukoglu¹

Department of Pediatrics, E. Wolfson Hospital, Holon, Israel; Research Institute, College of Judea and Samaria, Ariel¹, Institute of Endocrinology, Sourasky Medical Center, and Tel-Aviv University, Sackler School of Medicine, Tel-Aviv, Israel

Hanukoglu A, Fried D, Nakash I, Hanukoglu I. Selective increases in adrenal steroidogenic capacity during acute respiratory disease in infants. *Eur J Endocrinol* 1995;133:552–6. ISSN 0804-4643

To examine steroidogenic responses of the different zones of the adrenal cortex to acute disease we determined the basal and adrenocorticotropin (ACTH)-stimulated levels of cortisol, dehydroepiandrosterone (DHEAS) and aldosterone in 16 infants aged 1–4 months with acute bronchiolitis. Fourteen of the infants were retested after recovery. During illness the mean basal levels of cortisol and DHEAS were twice as high as the levels after recovery (370 vs 180 nmol/l and 2.7 vs 1.3 μ mol/l, respectively). The mean peak ACTH-stimulated levels of cortisol and DHEAS during illness were 1.5- and 2.5-fold higher, respectively, than the levels found after recovery. Although aldosterone secretion was stimulated ≥ 3 -fold by ACTH, illness was not associated with any change in aldosterone secretory capacity. The basal and stimulated levels of both cortisol and DHEAS during illness and after recovery were correlated significantly. Thus, the relative steroidogenic capacities for these two steroids were characteristic of the individual infant and showed constancy over a period of at least several weeks. While the levels of cortisol and aldosterone were not dependent on the age of the infants, both the basal and stimulated levels of DHEAS correlated strongly with age. We conclude that during acute disease the steroidogenic capacity selectively increases in the zones that secrete cortisol and DHEAS (only in infants <3 months) but not in the zona glomerulosa that secretes aldosterone. The DHEAS response may be related to its putative effects to enhance immune responses.

Aaron Hanukoglu, Department of Pediatrics, E. Wolfson Hospital, Holon 58100, Israel

A major response of the body to stressful conditions and inflammatory disease is the activation of the hypothalamus–pituitary–adrenal axis, leading to elevation of circulating levels of ACTH and glucocorticoids (1). Cortisol response during acute illness has been characterized in adults (2, 3) and pediatric age groups (4, 5). However, there is little information on the response of the different zones of the adrenal cortex during the first months of life (6, 7) when the adrenal cortex undergoes major developmental changes (8, 9). This study examined adrenal steroidogenic responses during this developmental period in both healthy infants and patients with acute bronchiolitis, a common respiratory disease of infancy.

Subjects and methods

The main study population of this report included 16 infants (11 male and 5 female) aged 1–3.5 months (mean \pm SD: 2.2 ± 0.8 months) who were admitted to hospital between November 1989 and March 1992 with a diagnosis of acute bronchiolitis, which is a viral lower respiratory tract infection. In all patients the diagnosis was based on the following criteria: acute onset of respiratory distress, respiratory rate >40 , expiratory wheezes or rales of auscultation, no previous

history of respiratory disease and occurrence during winter epidemics. Nine of the 16 infants were cyanotic in room air on admission, with a partial pressure of CO_2 in capillary blood (PaCO_2) >42 mmHg or transcutaneous oxygen saturation (SaO_2) $<90\%$. These infants required O_2 therapy and were defined as severe patients (10). The remaining seven patients, who also presented with tachypnea and wheezing, had no cyanosis. Their PaCO_2 was <42 mmHg and their SaO_2 was $>90\%$. These patients were defined as mildly affected patients. Normal PaCO_2 in infants is 27–41 mmHg (11). Unless specified otherwise, all the patients (mild and severe) were analyzed together.

Blood samples for the assay of basal hormone levels were drawn via a peripheral vein at 08.30–10.00 h. The ACTH stimulation test then was performed by rapid iv infusion of 0.25 mg of ACTH(1–24) and blood samples were collected from another vein 30 and 60 min after ACTH. The test was performed at an average of 2 days after the onset of respiratory distress. Fourteen of the 16 infants were retested after recovery within 10–21 days and one infant after 1 month (mean = 15 ± 3.4 days). Infants who recovered served as their own controls.

Most of the patients did not receive any therapy that might affect fluid and electrolyte balance. Only two

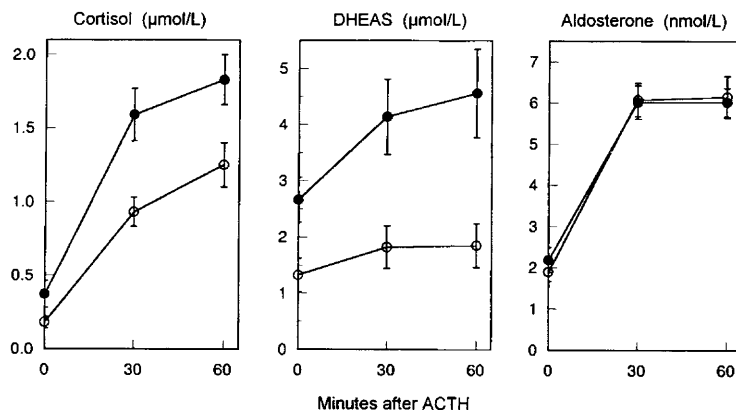


Fig. 1. Basal and ACTH-stimulated levels of cortisol, dehydroepiandrosterone (DHEAS) and aldosterone during illness (●) and after recovery (○). The mean cortisol and DHEAS values during illness were significantly different from the values during recovery ($p < 0.001$; except for cortisol at time zero, $p < 0.05$) as determined by Student's *t*-test for paired samples.

patients received maintenance iv fluids during the iv ACTH test. None of the patients received steroid therapy during the illness that is contraindicated in bronchiolitis and the electrolyte values in the ill infants did not differ significantly from that in recovered infants.

Because the recovered infants were 10–21 days older at retesting and dehydroepiandrosterone (DHEAS) levels were found to be influenced strongly by the age of the patients, especially in infants younger than the age of 3 months, the ACTH stimulation test was also performed in a third group of nine healthy infants aged 1–3 months (eight between 1 and 2 months of age and one at 3 months of age). Thus, the influence of age on DHEAS levels was analyzed in sick, recovered and healthy infants.

The study protocol was approved by the hospital's ethics committee and informed consent was obtained from all parents. Plasma steroid levels were determined

in duplicate by RIA kits (aldosterone kit from International CIS, Compagnie Oris Industrie, France; cortisol and DHEAS kits from Diagnostic Products Co., Los Angeles, CA). The paired samples (during illness and after recovery) from each patient were run on the same assay.

The significance of difference between values during illness and after recovery was examined by Student's *t*-test for paired samples. Unless indicated otherwise, the significance of the differences noted was $p < 0.01$. The data are presented as mean \pm SEM. The influence of age on steroid levels was analyzed by linear regression analysis.

Results

During illness the mean basal levels of cortisol (370 ± 90 nmol/l) and DHEAS (2.7 ± 0.4 μ mol/l)

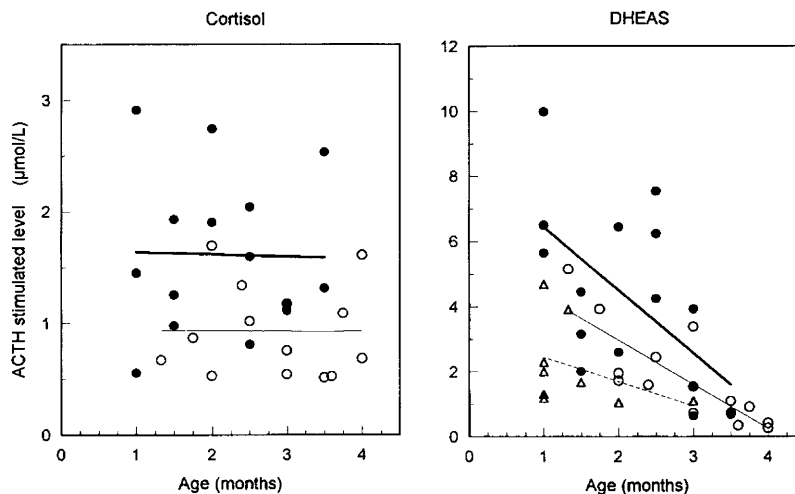


Fig. 2. Age dependence of cortisol and dehydroepiandrosterone (DHEAS) levels in ill (●, thick lines), recovered (○, thin lines) and healthy (△, dotted line) infants 30 min after ACTH stimulation. The lines represent the linear regression fits to data.

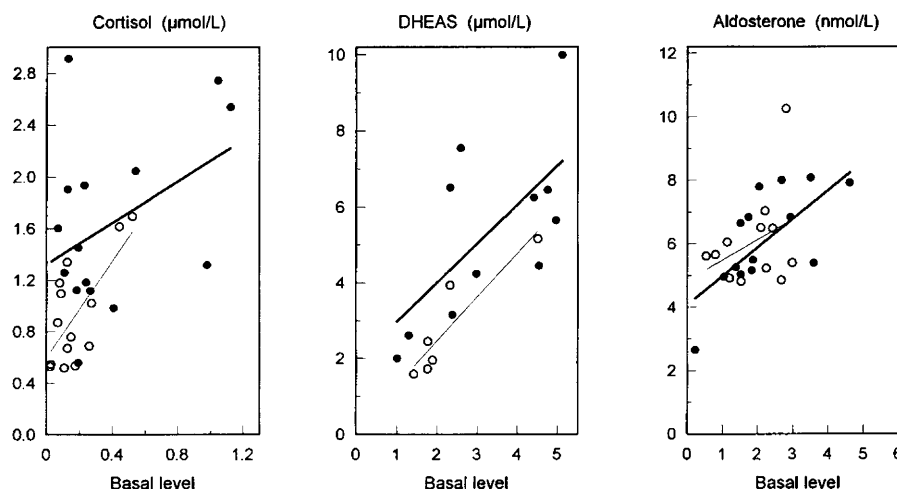


Fig. 3. Responsiveness of the adrenal cortex to ACTH stimulation during illness (●, thick lines) and after recovery (○, thin lines). The lines represent the linear regression fits to data. The dehydroepiandrosterone (DHEAS) values are shown only for infants younger than 3 months of age because of the age dependence (see Fig. 2). The ACTH-stimulated levels shown are the 30-min values. The correlation coefficients (r) during illness and after recovery were, respectively: for cortisol, 0.46 and 0.70; for DHEAS, 0.66 and 0.91; for aldosterone, 0.71 and 0.35 (for all r values >0.6 , $p < 0.01$).

were nearly twice as high as the post-recovery levels, while aldosterone levels showed no change (Fig. 1). The mean basal levels of cortisol (180 ± 40 nmol/l) and aldosterone (1.9 ± 0.2 nmol/l) in recovered children were in the range of previously reported values for healthy infants (12–14). The mean basal levels of DHEAS both in recovered (1.32 ± 0.3 µmol/l) and healthy (1.49 ± 0.2 µmol/l) infants were comparable with the levels in infants 1–12 months of age published by others (6, 12) but higher than those in another study (15). There was no sex difference in the mean levels of the three steroids. The basal levels of cortisol and aldosterone were correlated in ill infants ($r = 0.68$, $p < 0.01$). However, the basal levels of DHEAS were not correlated with the other two steroids either during illness or after recovery.

Comparison of the cortisol values for the two groups of severity of illness revealed that while the basal cortisol levels of the mild cases were in the range of infants after recovery, the cortisol levels of the severe cases were more than three times higher (160 ± 30 vs 530 ± 130 nmol/l). Thus, the illness-related difference in basal cortisol levels was contributed mainly by the severely ill patients. In contrast to cortisol, mean basal DHEAS levels were elevated similarly in both the mild and severe groups.

After ACTH administration in recovered infants, the mean levels of cortisol, DHEAS and aldosterone rose to about sevenfold, 1.5-fold and threefold higher than the respective basal values (Fig. 1). In ill infants, ACTH-stimulated levels of cortisol and DHEAS were about 1.5- and 2.5-fold higher than the values of recovered infants. Aldosterone levels did not show any illness-related difference.

While the basal levels of cortisol and aldosterone were not dependent on the age of the infants, the basal DHEAS levels showed a significant decrease by age (for recovered infants: $r = -0.88$, $p < 0.001$) (data not shown). The DHEAS response to ACTH stimulation also decreased with age in both ill and recovered infants below the age of 3 months (Fig. 2).

To examine the ACTH responsiveness of the adrenal, we compared the basal and ACTH-stimulated levels of the steroids. All three steroids showed a strong correlation between the basal and ACTH-stimulated levels, both in ill and recovered infants (Fig. 3). Although there was a significant overlap between the basal levels of steroids in recovered and ill infants, even the infants with low basal value showed a stronger responsiveness to ACTH during illness.

Basal levels of cortisol and DHEAS in recovered infants correlated strongly ($r = 0.77$ and $r = 0.78$, respectively; $p < 0.001$) with ACTH-stimulated levels of the same steroids during illness. Aldosterone values showed no similar correlation ($r = 0.14$). Thus, basal cortisol and DHEAS values in recovered infants could be used to predict adrenal responsiveness during illness.

Discussion

The present findings demonstrated that during acute respiratory illness in infants the capacity for the synthesis of both cortisol and DHEAS increased, while aldosterone biosynthetic capacity did not change. Based on an increase in plasma renin activity in a subgroup of infants with bronchiolitis, it was suggested that aldosterone levels might rise in this disease (16). Yet, our patients did not exhibit elevated levels of aldosterone.

The three steroids that we have examined are synthesized in three different zones of the adrenal cortex: cortisol in the permanent zone, which develops into adult zona fasciculata; DHEAS in the remnant of the fetal zone; and aldosterone in the outermost zona glomerulosa. The lack of correlation between cortisol and DHEAS levels suggests that the regulation and the sites of synthesis of these two adrenal steroids are independent.

The fetal (inner) zone, which constitutes 80–90% of the adrenal gland during late gestation (9), undergoes involution during early infancy (8). The capacity for DHEAS synthesis and secretion declines during the first year of life (6, 17–20). Our findings of the high basal levels of DHEAS, its strong acute rise in response to ACTH and, most significantly, the change in the capacity for its biosynthesis during illness demonstrate that this zone remains functionally active during the first 3 months of life.

The steroidogenic capacity is generally determined by the levels of steroidogenic enzymes (21). Adrenocorticotropin can enhance the expression of these enzymes in adrenocortical cells 24–48 h after stimulation (21, 22). The overstimulation of the hypothalamus–pituitary–adrenal axis during illness probably exerts a similar effect, leading to a rise in adrenal steroidogenic capacity. The patients examined here suffered from respiratory distress for an average of 2 days, a period that would be sufficient for a rise in enzyme levels in the cells that synthesize cortisol and DHEAS but not for a change in adrenal tissue growth.

The basal and stimulated levels of each of three steroids examined showed significant correlation during illness or after recovery. Thus, the basal levels of steroids reflected the capacity of the adrenal to respond to ACTH stimulation. One study in adults reported an inverse correlation between basal and stimulated levels of cortisol (23). This finding was interpreted to show a depletion of precursor stores (23). Our finding of a positive correlation unequivocally shows that in infant adrenals the precursor was not depleted. On the contrary, the higher basal levels were indicative of higher steroidogenic capacity. Another study in adult women found no correlation between the basal and ACTH stimulated levels of adrenal steroids (24).

Although after recuperation the levels of cortisol and DHEAS returned to the normal range, the illness versus post-recovery values for both cortisol and DHEAS remained highly correlated. Hence, the relative steroidogenic capacity for these two steroids was characteristic of the individual infant and remained constant over a period of at least several weeks. These findings are consistent with the results of a study on twins on the heredity of cortisol responses to non-disease stress situations (25).

The cortisol response to stress and disease is an important function of the neuro-immune-endocrine system. The fact that DHEAS capacity also rose during

acute illness only in infants <3 months suggests that DHEAS may have a special role at this stage of development when the immune system is still immature. Dehydroepiandrosterone may enhance immune functions and can protect against acute lethal viral infections (26, 27).

In our patients, both basal and ACTH-stimulated levels of cortisol were linked with the severity of illness. The lack of a beneficial effect of systemic glucocorticoid treatment in the treatment of bronchiolitis (28) suggests that the physiological glucocorticoid response of the body may be sufficient. However, three of our patients had persistently low cortisol levels (<100 nmol/l) even after recovery. Two of them (twin babies) showed normal basal levels only at their third examination at the age of 7 months (data not shown). These observations and the low basal cortisol levels found in a subgroup of babies (19, 29) suggest that in some infants the low basal cortisol may reflect the immaturity of the permanent zone. It remains to be determined whether infants with low basal levels may benefit from temporary glucocorticoid treatment during illness. The significant correlation between the basal and stimulated levels of cortisol and DHEAS indicate that the basal levels of these steroids can provide an index for the prediction of the steroidogenic responsiveness of infants during illness.

Acknowledgments. We are grateful to Dr Myriam Tuval and Mrs Irit Benyovits for excellent technical assistance and to Mrs Diklah Geva for statistical analysis. This research was supported in part by a grant from The Ministry of Health to AH.

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Received May 15th, 1995

Accepted June 6th, 1995