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Thyrotropin and prolactin response to thyrotropin-releasing hormone in healthy and asphyxiated full-term neonates

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To evaluate the effect of perinatal asphyxia on the pituitary response to thyrotropin-releasing hormone (TRH) in full-term newborn infants, serum thyrotropin (TSH) and prolactin (PRL) levels were measured before and 30 and 180 min after i.v. administration of 40 μg TRH. Birth weight, gestational and postnatal age were similar in the healthy (group NA) and in the asphyxiated (group A) babies. Hormone levels were determined by radioimmunoassay using commercial kits.

It was demonstrated that the basal TSH level was slightly higher and the basal PRL level significantly ($p < 0.05$) higher in group A than in group NA. In response to TRH administration in group A a marked increase in PRL occurred from 6781 $\pm$ 887 to 11 072 $\pm$ 1318 and 9636 $\pm$ 1024 mU/l at 0, 30 and 180 min, respectively. A similar response was seen in group NA; the values, however, remained significantly lower during the TRH-test. The respective PRL values at 0, 30 and 180 min were 4672 $\pm$ 411, 7945 $\pm$ 343 ($p < 0.05$) and 5963 $\pm$ 372 mU/l ($p < 0.05$).

TRH administration also resulted in a significant elevation of the serum TSH level from 6.20 $\pm$ 1.30 to 49.02 $\pm$ 7.25 ($p < 0.01$) and 18.72 $\pm$ 6.35 mU/l ($p < 0.05$) in group A, and from 3.90 $\pm$ 0.57 to 24.01 $\pm$ 3.81 ($p < 0.01$) mU/l in group NA, but in group NA the 180 min TSH value of 6.07 $\pm$ 1.25 mU/l did not differ statistically from the basal level ($p > 0.1$).

It is concluded that the pituitary PRL and TSH reserves are maintained in full-term newborn infants recovering from perinatal asphyxia whose biochemical findings are indicative of subclinical hypothyroidism.

Neonatal serum TSH undergoes a sharp rise after birth reaching the peak at 30 minutes. This is followed by a rapid decline during the first 24 h and then a much slower decrease over the next two days [6, 7]. This pituitary response appears to be stimulated by cooling the extrauterine environment. High prolactin (PRL) values have also been found in newborn infants [13, 23] and since the rise in PRL secretion is associated with a concomitant increase of serum TSH, it has been hypothesised that during the early period of life there is a TRH surge which releases both TSH and PRL [23]. Jacobsen et al. [15, 16] found that in the first week of life the relative responses of serum TSH to TRH in euthyroid full-term, preterm and small-for-gestational age newborns were equal to that of adults and older children [2, 8, 14]. More recently Delitala et al [3, 4] applying TRH stimulation tests could demonstrate an adequate neonatal PRL and

TSH reserve despite the high basal PRL and TSH values found in human neonates.

In view of the observation that hypoxia decreases thyroid function [9, 20] whereas it does not cause any significant change in the plasma PRL level in fetal sheep [19], the present study was undertaken to evaluate the basal TSH and PRL levels and their response to TRH stimulation during the early neonatal period in healthy and asphyxiated full-term neonates.

Materials and Methods

Studies were carried out in 11 asphyxiated and 11 healthy full-term newborn infants. The asphyxiated infants (group A) had a mean birth weight of 3211 g (range, 2970–3500 g) and mean gestational age of 39.0 weeks (range, 38–40 weeks). The birth weight and gestational age of infants of the non-asphyxiated group (group NA) ranged from 2890 to 3500 g (mean, 3264 g) and from 38 to 41 weeks (mean, 39.5 weeks), respectively.

Gestational age was calculated from the mother's menstrual history and was confirmed by physical examination of the infants. All were full-term with appropriate weight for dates.

The infants were born after uncomplicated pregnancy and normal vaginal delivery.

Asphyxiated infants had a one-minute Apgar score of ≤ 6 and mean actual pH of 7.12 (range, 7.03–7.18) requiring O_2 administration for several hours, but all were in a good condition during the period of investigation.

Infants of group NA had Apgar scores of more than 7 at one-minute of age and after the routine care in the delivery room they remained well during the whole neonatal period.

None of the mothers had received drug therapy known to influence thyroid function and their family history did not reveal thyroid disorders.

Determinations were performed at mean postnatal ages of 97 h and 95.2 h in groups A and NA, respectively.

In order to eliminate the possible influence of a circadian TSH and PRL rhythm, all tests were started at 9.00 a.m. while the infants were kept in thermally controlled environment.

Synthetic TRH (Hoechst GA) was administered intravenously in a dose of 40 μg. Blood samples were obtained prior to and 30 and 180 min after TRH injection. Blood was centrifuged immediately and serum stored at -20 °C until analysis. Serum TSH was measured by RIA using Amersham kits according to the method of Martin and Landon [18]. Serum PRL measurements were also made by RIA using commercial kits manufactured by Serono.

Informed parental consent was obtained for the study.

The results were expressed as mean $\pm$ SE and statistical evaluation was done by using Student's t-test. When necessary the coefficient of correlation and the equation of regression were also calculated.

Results

Clinical data and the results of TRH-test in infants with and without perinatal asphyxia are given in detail in Tables I and II.

Changes in mean serum TSH and PRL levels in response to TRH administration are shown in Fig. 1 *(a, b)*. It can be seen that the basal TSH level was slightly higher and the basal PRL level significantly ($p < 0.05$) higher in group A than in group NA. In response to TRH administration in group A a marked increase occurred in PRL from 6781 $\pm$ 887 to 11072 $\pm$ $\pm$ 1318 and 9636 $\pm$ 1024 mU/l at 0, 30 and 180 min respectively. A similar response was seen in infants of group NA, the values, however, remained significantly lower during the TRH-test. The respective PRL values at 0, 30 and 180 min were 4672 $\pm$ 411, 7945 $\pm$ 343 ($p < 0.05$) and 5963 $\pm$ $\pm$ 372 mU/l ($p < 0.05$), respectively.

TABLE I

Clinical data and the results of TRH-test in infants with perinatal asphyxia

No.	Sex	Gestational age weeks	Birth weight g	Postnatal age h	Apgar score		TRH-test					
							Se-PRL, mU/l			Se-TSH, mU/l		
					1	5	0	30	180	0	30	180
					min		min					
1	M	39	3 450	96	3	9	9 200	16 000	9 200	9.2	46.8	11.9
2	M	38	2 970	88	1	9	10 600	16 800	12 200	4.2	13.4	4.6
3	M	38	3 250	98	4	9	9 800	12 800	14 000	3.4	58.0	70.0
4	F	38	3 290	108	5	8	11 000	16 800	16 200	5.2	64.0	12.0
5	F	40	3 330	90	6	9	4 000	13 200	10 600	4.8	70.4	12.0
6	F	39	3 500	87	6	8	6 800	7 800	7 800	3.1	20.0	6.1
7	F	38	3 120	91	1	9	2 800	6 000	6 000	7.6	42.1	5.2
8	F	40	3 150	103	6	9	6 000	7 400	7 000	18.0	62.0	46.0
9	F	40	3 030	107	4	8	6 000	7 000	6 800	4.6	74.0	22.0
10	M	39	2 980	95	3	9	4 800	6 000	6 000	4.4	76.0	12.0
11	M	40	3 260	104	3	9	3 600	12 000	10 200	3.8	12.6	4.1

TABLE II

Clinical data and the results of TRH-test in infants without perinatal asphyxia

No.	Sex	Gestational age weeks	Birth weight g	Postnatal age h	Apgar score		TRH-test					
							Se-PRL, mU/l			Se-TSH, mU/l		
					1	5	0	30	180	0	30	180
					min		min					
1	M	40	3 170	96	9	10	3 600	7 800	4 400	3.6	17.4	7.2
2	M	41	3 300	84	9	10	3 600	7 200	5 000	8.4	50.2	11.6
3	F	40	3 500	86	9	10	6 800	8 800	7 000	4.8	40.0	9.2
4	F	40	3 160	98	9	10	3 200	6 200	4 600	2.4	24.0	7.4
5	F	40	3 130	108	9	10	6 000	9 200	5 400	4.2	36.0	10.5
6	F	39	3 500	90	9	10	4 400	8 800	8 000	3.2	15.4	2.2
7	M	40	3 470	88	9	10	3 200	7 200	4 600	1.8	24.0	1.8
8	F	38	2 890	90	9	10	4 400	7 800	6 600	3.6	16.0	2.4
9	F	40	3 140	98	9	10	6 000	7 600	6 800	4.1	12.0	11.0
10	M	39	3 270	104	9	10	3 800	6 800	6 200	1.5	16.5	2.0
11	M	38	3 380	106	9	10	6 400	10 000	7 000	5.4	12.7	1.5

TRH administration also resulted in a significant elevation of serum TSH level from 6.20 ± 1.30 to 49.02± ± 7.25 ($p < 0.01$) and 18.72 ± 6.35 mU/l ($p < 0.05$) in group A, and from 3.90 ± 0.57 to 24.01 ± 3.81 mU/l ($p < 0.01$) in group NA, but in group NA the 180 min TSH value of 6.07 ± 1.25 mU/l did not differ statistically from the basal level ($p < 0.1$).

Figure 2*a* demonstrates a significant positive relationship of TSH to PRL during TRH stimulation test ($r = 0.52$ $p < 0.01$) indicating that the common hypothalamic control mechanism was functioning in healthy neonates.

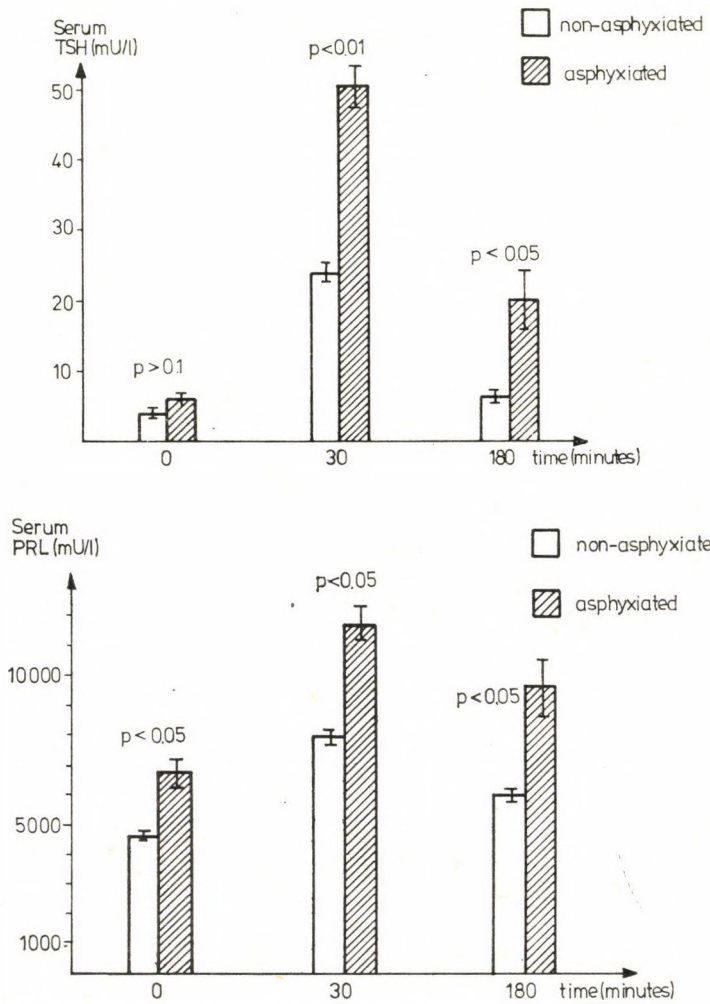

FIG. 1. Serum PRL *(a)* and TSH *(b)* response to TRH administration in healthy and asphyxiated full-term newborn infants

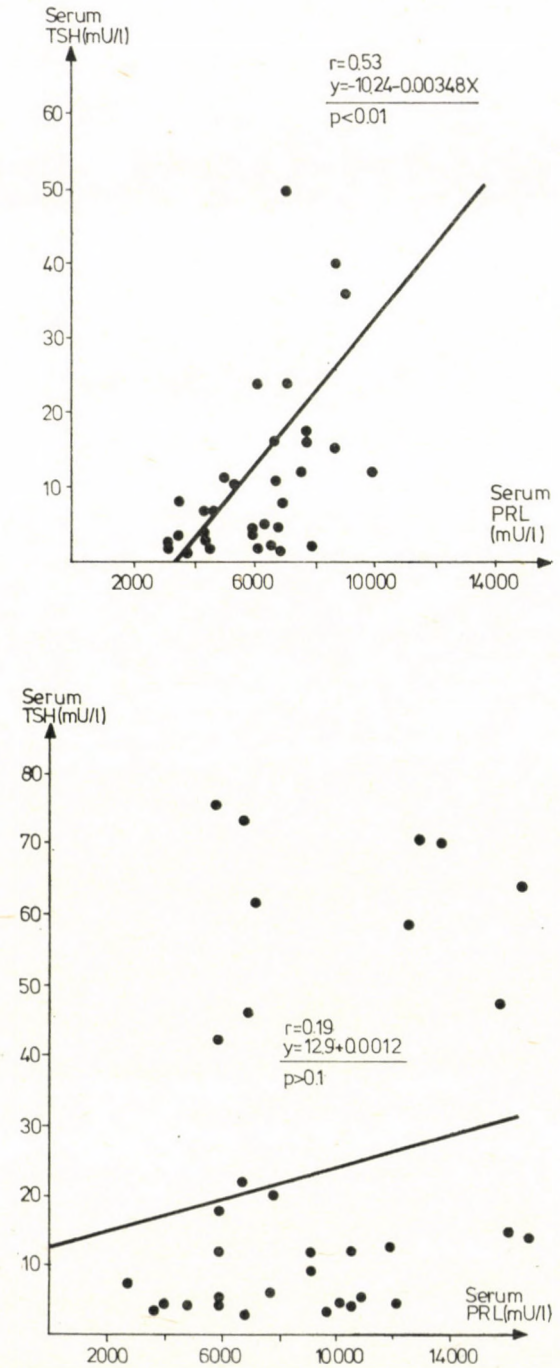

FIG. 2. Relationship between serum TSH and PRL during TRH stimulation test in healthy and asphyxiated full-term newborn infants

In asphyxiated newborn infants this relationship could not be seen (Fig. 2*b*). This finding may be interpreted as showing that perinatal hypoxia modulates differently the pituitary TSH and PRL secretion in response to TRH.

Discussion

The present results are in good agreement with the previous finding of normal pituitary reserves of TSH and PRL in human newborn infants [4, 11, 15, 16].

Prior to TRH administration the basal values of TSH did not differ in the asphyxiated neonates from those in healthy infants. Few data are available as to the influence of hypoxia on TSH secretion. Moshang et al [20] reported low serum TSH and normal T_3 and T_4 levels in children with acute hypoxia and a slightly elevated TSH and significantly depressed T_3 and T_4 levels in those with chronic hypoxia. These findings have been regarded to indicate the adaptation of the hypothalamic-pituitary-thyroid axis to hypoxia in order to increase the resistance to hypoxia by the hypothyroid state [9, 26].

Similarly, a transient elevation of TSH and a significant decrease of the thyroxine level were observed in newborn infants with respiratory distress syndrome [21, 24]. It is reasonable to speculate that the impaired thyroid function associated with hypoxaemia may be a defence mechanism to decrease the metabolic rate and oxygen consumption in newborn infants whose oxygenization is compromised [17].

Jacobsen et al [15] also reported higher TSH levels in asphyxiated neonates but those infants were delivered by Caesarean section and it is difficult to say whether it was the surgical delivery itself or the underlying conditions that contributed to the rise of serum TSH [5].

Neonatal TRH challenge tests were performed by Jacobson et al [15, 16] and by Delitala et al [4]. Their results are in agreement with the present ones in that in healthy newborns the relative TSH response to TRH was equal to that of adults in spite of the elevated basal TSH concentration.

A further important point in our study was the demonstration of elevated serum PRL in newborn infants, in particular in those who had recovered from perinatal asphyxia.

The clinical significance of the high serum PRL is not completely understood [1, 13, 23]. The findings presented by Smith et al [25] and Gluckmann et al [10] seem to indicate that PRL may contribute to maturation of the fetal lung by demonstrating a significantly lower cord PRL concentration in premature infants who developed respiratory distress syndrome than in those who did not suffer from RDS. Furthermore, Grosso et al [12] found higher PRL levels in infants delivered by pre-eclamptic women than in those delivered by normotensive women, suggesting that chronic fetal distress associated with

pre-eclampsia may induce increased fetal PRL production.

PRL is generally regarded as a stress hormone [22, 23] and its high values in the immediate neonatal period may be considered a non-specific pituitary response to labour and delivery as a stress. Perinatal asphyxia means a further stress and may account for the significantly higher PRL levels found in asphyxiated neonates.

In response to TRH stimulation the PRL response was unaltered in spite of the high base-line level. This observation indicates that perinatal asphyxia does not impair the pituitary PRL reserves.

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