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Spontaneous changes in growth hormone and insulin levels in newborn infants

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Ten term, normally grown newborn infants aged 3—5 days with hyperbilirubinaemia due to rhesus or ABO incompatibility have been studied. Blood samples were taken via an umbilical venous catheter at 10 minute intervals in order to study spontaneous changes in growth hormone, insulin, glucose and free fatty acid concentration. Mean plasma GH, insulin and glucose concentrations remained unchanged, but the FFA level rose, due probably to the low room temperature at which the investigations were performed.

Analysis of individual changes showed large and bidirectional alterations in GH and insulin, which were much greater than the error of the analytical methods. The findings should be considered in the evaluation of diagnostic investigations performed on newborn infants.

Since the development of insulin radioimmunoassay by Berson and Yalow [2], the hormonal control of metabolic adaptation has become a much researched aspect of neonatology.

In interpreting hormonal changes of any kind in the newborn infant, the knowledge of basal hormone concentrations is of fundamental importance. Despite many efforts certain questions still seem to be unanswered. It is clear from the pertaining literature that the basal levels of different hormones vary remarkably in spite of the fact that the patients studied seem to be homogeneous. Although methodological differences and errors may in part explain the wide variations, two more possibilities must be considered, *viz.* (i) the patients are not as homogeneous as was thought on clinical grounds; (ii) the patients are homogeneous but there are spontaneous fluctuations of the hormone concentrations.

In order to prove or disprove the latter possibility, we have studied in newborn infants the spontaneous changes in growth hormone (GH) and insulin concentration and also the simultaneous alterations of the blood glucose and free fatty acid (FFA) levels.

Patients and Methods

Ten full term (gestational age $\geq$ 37 weeks), normally grown (birth weight percentile 10—90) newborn infants aged 3—5 days with hyperbilirubinaemia due to rhesus or ABO incompatibility have been studied (Table I). The pregnancy was complicated by pre-eclampsia in two cases,

TABLE I

Clinical data of patients

No.	Birth weight (g)	Gestational age (week)	Percentile weight	Postnatal age (days)	Pregnancy history	Delivery	Incompatibility
1	3500	39	75	3	uneventful	spontaneous	Rh
2	2380	37	10—25	5	uneventful	spontaneous	Rh
3	2880	38	25—50	4	toxaemia	spontaneous	ABO
4	2750	37	25—50	4	toxaemia	spontaneous	ABO
5	2970	40	10—25	5	uneventful	Caesarean	Rh
6	3100	40	25—50	3	uneventful	spontaneous	Rh
7	3720	40	75—90	3	uneventful	spontaneous	ABO
8	2920	39	10—25	3	uneventful	spontaneous	Rh
9	3140	39	25—50	4	uneventful	spontaneous	Rh
10	3400	41	50—75	3	uneventful	spontaneous	Rh

while it was uneventful in the others. One infant was born by Caesarean section for maternal reasons, the others by normal spontaneous delivery. None needed resuscitation and the 5 minute Apgar score was 7 or higher. Seven babies suffered from rhesus incompatibility and three from ABO incompatibility of mild or moderate degree. No sign of neurological damage could be detected in the infants either on admission or subsequently. Exchange transfusions were decided on clinical grounds because of the high bilirubin level in relation to postnatal age.

For exchange transfusion an umbilical vein catheter was introduced 5—7 cm high and then fixed. Blood was taken via the catheter for GH, insulin, glucose and FFA analysis at 10 minute intervals for one hour. To prevent obstruction, the catheter was flushed with physiological sodium chloride solution a few times.

Exchange transfusions were performed at 23—25°C room temperature. The babies were covered with sterile sheets, no "baby heater" was used. During the investigation all infants remained quiet, though from time to time some muscular activity could be observed. Before starting the transfusion, 20 ml blood was taken and then the exchange transfusion was begun by injecting 20 ml blood. The last meal was ingested three hours before the 60 min sample. All transfusions were done between 2 and 7 p. m.

Blood was collected in heparinized tubes and centrifuged immediately after sampling. Plasma for hormone assays was stored at —20°C and thawed only once.

Blood glucose concentration was estimated by the method of PRYCE [29], FFA by a combination of the methods of DALTON and KOWALSKI [6] and LAURELL and TIBBLING [21], and insulin by the method of HALES and RANDLE [13]. GH concentration was estimated by a double antibody method (Growth Hormone Binding Reagent, Wellcome Reagents Ltd.). The error or the GH and insulin assays was ±10%.

RESULTS

Growth hormone (Table II). There was a gradual fall in the mean plasma GH concentration during the period of study (Fig. 1). This was 13 ng/ml at 60 minutes, or a fall of 26% from

TABLE II

Spontaneous changes in plasma GH and insulin in newborn infants

No.	0	10	20	30	40	50	60 minutes
Growth hormone, ng/ml							
1	45	32	26	17	16	18	15
2	23	23	25	31	30	27	26
3	29	28	34	32	25	22	20
4	29	27	24	24	25	22	25
5	10	7	9	8	6	6	7
6	58	51	44	35	32	18	16
7	8	9	7	5	7	6	7
8	18	18	25	27	27	27	25
9	64	60	42	36	33	33	28
10	—	—	—	—	—	—	—
mean	*32*	*28*	*26*	*24*	*22*	*20*	*19*
± SE	5.9	5.2	3.8	3.4	3.0	2.7	2.3
Insulin, micro U/ml							
1	48	61	73	52	58	80	120
2	31	24	15	14	15	15	12
3	—	—	—	—	—	—	—
4	30	25	23	25	20	21	24
5	18	18	23	4	16	13	13
6	29	15	32	39	15	60	21
7	9	9	4	5	5	4	4
8	19	13	11	5	5	11	13
9	38	28	30	40	39	29	25
10	39	28	23	5	18	21	11
mean	*29*	*25*	*26*	*21*	*21*	*28*	*27*
± SE	4.0	5.2	6.0	6.1	5.6	9.4	11.8

the original mean level (Table IV), but the change was not significant statistically due to the wide scattering. Analysis of individual results showed marked oscillations of the plasma GH value, which exceeded the error of the method (Fig. 2).

Insulin (Table II). No significant change was observed in the mean plasma insulin level during the observation period (Fig. 1). The maximum deviation from the initial value occurred at 30 minutes; it was 8 micro U/ml or 35% (Table IV). Ex-

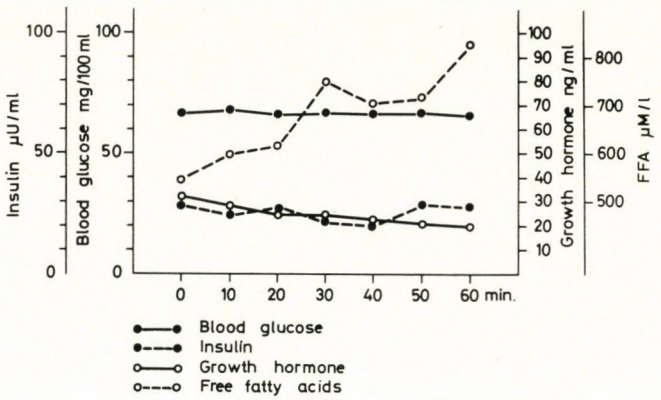

FIG. 1. Mean plasma concentration of GH, insulin, glucose and FFA in newborn infants at ten minute intervals during one hour. Standard errors see in Tables II and III

amination of individual cases showed changes as great as +150 and −88% (Fig. 3).

Glucose (Table III). The mean blood glucose level remained steady; the changes did not exceed ±1 mg/100 ml or 2% (Table IV). On individual analysis some considerable changes were detected, mainly in the second half of the observation period but these were much smaller than the changes occurring in the GH and insulin levels.

Free fatty acids (Table III). In the mean FFA concentration a marked rise was observed; its degree varied greatly from case to case and occasionally a fall also occurred.

No significant correlation was found between the changes of the GH, insulin, glucose and FFA concentrations.

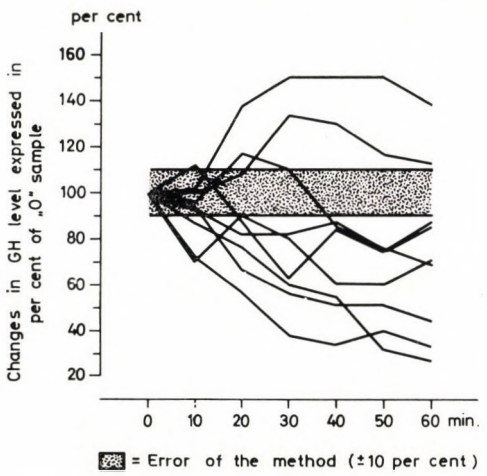

FIG. 2. Percentual changes in plasma GH in newborn infants (100 per cent = initial concentration)

TABLE III

Spontaneous changes in blood glucose and FFA in newborn infants

No.	0	10	20	30	40	50	60 minutes
Glucose, mg/100 ml							
1	65	61	60	62	63	66	67
2	63	62	59	68	65	69	68
3	96	101	95	93	88	84	79
4	83	81	75	75	73	75	76
5	57	57	56	52	53	52	51
6	51	52	54	54	63	63	66
7	41	41	41	43	47	45	47
8	70	62	59	56	57	57	58
9	78	78	80	76	78	77	76
10	69	83	83	92	82	82	75
mean	*67*	*68*	*66*	*67*	*67*	*67*	*66*
±SE	5.1	5.6	5.2	5.4	4.2	4.7	3.5
FFA — micro M/l							
1	750	1230	1380	1180	1260	1150	1230
2	800	600	480	740	450	488	830
3	197	114	370	660	100	114	550
4	155	187	180	202	284	330	158
5	450	640	695	800	1070	1180	1060
6	280	370	480	885	940	865	1120
7	850	650	775	1090	1060	1070	1090
8	155	110	160	114	139	135	120
9	800	970	775	1100	1090	1030	1040
10	1030	1060	875	720	680	820	1050
mean	*546*	*592*	*615*	*748*	*706*	*716*	*825*
± SE	108	128	117	115	140	134	130

DISCUSSION

GH and insulin can be detected in the human foetus as early as the second to third month of gestation [19, 32]. It is also well-known that the GH concentration both in the umbilical blood and in the newborn infant is much higher than that in the mother and considerably exceeds the values found in children and adults [4, 20, 38]. The ability of the foetus to increase its insulin secretion in response to a glucose load has been disputed in the literature [17, 23, 28, 36] but it is generally accepted

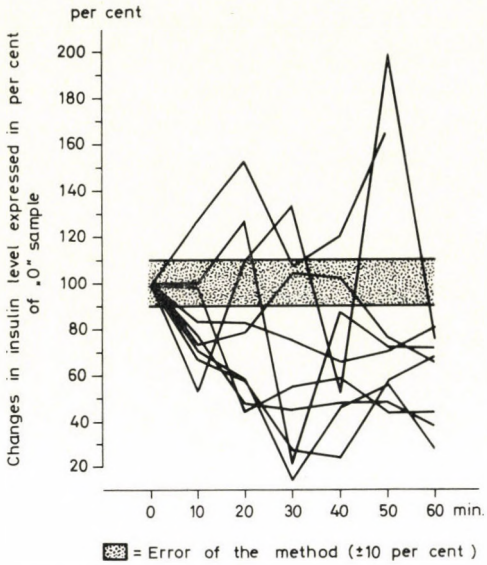

FIG. 3. Percentual changes in plasma insulin in newborn infants (100 per cent = initial concentration)

TABLE IV

Spontaneous changes in plasma growth hormone, insulin, glucose and free fatty acid, in per cents

	0	10	20	30	40	50	60 minutes
Growth hormone							
mean	*100*	*91*	*91*	*86*	*82*	*75*	*74*
± SE	—	4.6	8.2	12.6	12.6	12.5	12.2
Insulin							
mean	*100*	*83*	*84*	*65*	*67*	*88*	*79*
± SE	—	7.3	12.5	12.4	10.1	19.1	22.0
Glucose							
mean	*100*	*100*	*98*	*100*	*101*	*101*	*100*
± SE	—	2.7	3.0	4.5	4.4	4.4	4.7
Free fatty acids							
mean	*100*	*106*	*125*	*161*	*144*	*146*	*172*
± SE	—	11.4	14.5	29.5	29.2	28.2	33.0

that the newborn infant can do so, although the insulin response is sluggish, at least in the early postnatal period [1, 34]. Despite the fact that GH and insulin are important hormones with partly synergistic and partly antagonistic anabolic actions, their role in intrauterine growth and development is unclear. It has been suggested that GH is not essential for the development of optimum body weight and size [3, 18, 31] and the regulation of the foetal blood glucose level seems to be independent of foetal insulin secretion.

The present findings showed marked oscillations in the umbilical venous plasma GH and insulin concentrations estimated at 10 minute intervals for one hour. The variation was much greater than that of the analytical technique and therefore could not be ascribed to the method of assay. The mean values for the group tended to mask the individual alterations (Fig. 1) but the great standard errors (Tables II and III) reflected wide variations. The variations in plasma GH and insulin concentration can therefore be ascribed to alterations in secretion, distribution or degradation.

In children and adults GH secretion increases during fasting, muscular exercise and stress [7, 10, 11, 14, 30] whereas the effect of stress on GH secretion in the newborn is controversial [24, 35]. Blood samples were taken from an indwelling venous catheter to eliminate the possible effects of repeated venipunctures and muscular activity. In some of the infants, the plasma GH concentration fell gradually during the study period (Fig. 2). It arose that in these babies the initial plasma GH concentration was high due to the stress of umbilical catheterization but this idea was not supported by the observation that the mean GH concentration in scalp venous plasma 10 min before umbilical catheterization was 28 ± 5.9 ng/ml, not significantly different from that in the first umbilical venous sample, 32 ± 5.9 ng/ml. The infants were exposed to cold during the study since the room temperature was 23—25°C and this was probably responsible for the progressive rise in mean plasma FFA concentration, but cold exposure did not cause increased GH secretion, in agreement with earlier observations [9, 25].

No significant correlation was observed between the spontaneous changes in the GH, insulin, glucose and FFA levels. This finding may have relevance to the suggestions that circulating energy substrates such as glucose, FFA and amino acids exert an influence on GH and insulin secretion by positive or negative feed-back mechanisms [5, 8, 10, 11, 12, 22, 26]. While exogenous changes in metabolite concentration are affecting GH and insulin secretion in the newborn infant, the present results suggest that spontaneous changes in glucose and FFA do not influence GH and insulin concentrations within a 60 min period.

Spontaneous changes in plasma insulin in the newborn infant have

not been reported, but many workers have studied changes in plasma GH in adults and children during the day and also at night [15, 16, 27, 30, 33, 37]. It is well-established that GH secretion increases during deep sleep in children [15, 16] and adults [3], but SHAYWITZ et al. [33] observed rapid oscillations of wide amplitude in plasma GH concentration which were independent of sleep phases in term newborn infants.

It is unlikely that the changes in plasma insulin concentration in the individual infants observed in the present study could have resulted from changes in the position of the catheter tip, as this was not moved after its initial fixation.

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