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Research Article

Endocrine function has been investigated in four anencephalic neonates to determine the influence of absence of cortical and hypothalamic tissue and of hypoplasia of the pituitary. Intravenous glucose administration resulted in higher peak values for blood sugar and more rapid glucose disposal rates than reported in normals. Intravenous insulin tolerance tests on two of the infants failed to evoke elevations in plasma growth hormone, and the infants showed a remarkable resistance to the hypoglycemic effect of insulin. Administration of lysine-vasopressin caused an active growth hormone release. Similarly, there was a large increase in serum thyrotropin after administration of synthetic thyrotropin-releasing hormone. Basal levels of both thyrotropin and growth hormone were low as compared with values reported for normal newborns. Prolactin values obtained on three of the infants were in the normal range. The results strongly suggest that anterior pituitary function mediated by the hypothalamus and its releasing factors is deficient in anencephaly. However, the anterior pituitary can release growth hormone and thyrotropin when stimulated directly and, in the case of thyrotropin release, may function autonomously. The normal prolactin values presumably reflect the absence of the hypothalamic prolactin inhibitory factor.

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Endocrine Studies in Anencephaly

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ABSTRACT Endocrine function has been investigated in four anencephalic neonates to determine the influence of absence of cortical and hypothalamic tissue and of hypoplasia of the pituitary. Intravenous glucose administration resulted in higher peak values for blood sugar and more rapid glucose disposal rates than reported in normals. Intravenous insulin tolerance tests on two of the infants failed to evoke elevations in plasma growth hormone, and the infants showed a remarkable resistance to the hypoglycemic effect of insulin. Administration of lysine-vasopressin caused an active growth hormone release. Similarly, there was a large increase in serum thyrotropin after administration of synthetic thyrotropin-releasing hormone. Basal levels of both thyrotropin and growth hormone were low as compared with values reported for normal newborns. Prolactin values obtained on three of the infants were in the normal range. The results strongly suggest that anterior pituitary function mediated by the hypothalamus and its releasing factors is deficient in anencephaly. However, the anterior pituitary can release growth hormone and thyrotropin when stimulated directly and, in the case of thyrotropin release, may function autonomously. The normal prolactin values presumably reflect the absence of the hypothalamic prolactin inhibitory factor.

INTRODUCTION

Defects of neural tube formation that include anencephaly and meningocele are the most common major congenital anomalies in the United States (1). The incidence of these malformations ranges from 1 per 1,000 in the United States to as high as 5-6 per 1,000 in Irish populations. Although the etiology of anencephaly is unknown, the defect is probably due to polygenic influences on early de-

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velopment of the neural tube (2). A major clinical feature of anencephaly is prolonged gestation (3). Infants with anencephaly are of normal proportions but are generally under the 50th percentile for weight (4). Pathological studies reveal hypoplastic pituitaries and small adrenals, deficient in a fetal zone (5, 6). The thyroid, gonads, and the number of pancreatic islets appear to be normal (7), but β -cell hypertrophy is often seen (8). As complete absence of the hypothalamus is a feature of anencephaly (4), these infants offer an opportunity to investigate endocrine function in the absence of an intact hypothalamic-pituitary axis. We will report on endocrine studies in four such anencephalic infants.

METHODS

Four anencephalic infants, three females and a male, were included in the study. Birth weights ranged from 3.2 to 4.5 kg. Gestation was greater than 40 wk in all cases (43-47 wk). Three of the infants were delivered by cesarean section because of failure to induce labor. Maternal age was between 25 and 30 yr and three of the mothers were primigravidas. Hydramnios was documented in two cases. The infants died at 4 h (baby A), 35 h (baby B), 5 days (baby C) and 8 days of age (baby D). Permission to carry out the investigation was granted by both parents in each instance. Consent was obtained by the responsible obstetrician or pediatrician at the Boston Hospital for Women (Lying-In Division).

Initial studies were carried out within the first 12 h of life. An umbilical venous catheter was introduced to administer various agents and to obtain blood samples. This was left in place for the duration of the studies.

Intravenous glucose tolerance tests using a glucose load of 1 g/kg were carried out on infants A and B. Infants C and D were subjected to insulin tolerance tests with insulin doses of 0.2 U/kg and 1.0 U/kg, respectively. During the insulin tolerance tests, blood samples were collected every 10 min for 1 h for determination of glucose, growth hormone, and cortisol. The test was terminated by administration of 1 g/kg of glucose. Lysine-vasopressin (Sandoz [Sandoz Pharmaceuticals, Hanover, N. J.], 0.5 U/kg) was administered to the longer surviving infants (C and D), and blood samples were obtained for growth hormone and cortisol determinations. Synthetic ACTH (Organon, Inc.,

West Orange, N. J.) was also administered to babies C and D, and the cortisol response was determined 30 min later.

Synthetic thyrotropin-releasing hormone (TRH)¹ (generously provided by Dr. M. S. Anderson, Abbott Laboratories, North Chicago, Ill.) was administered to three of the infants within the first 8 h of age in order to investigate the pituitary thyroid-stimulating hormone (TSH) secretory response. Blood for TSH determination was obtained at 0 and 20 min in babies A and B and at 0, 10, 20, and 30 min after TRH (100 µg) administration in baby C.

The serum radioimmunoassay for serum TSH was carried out by a modification (9) of the method of Odell, Wilbur, and Utiger (10) and similar to that recently reported by Patel, Burger, and Hudson (11). TSH was labeled with ¹²⁵I (specific activity 50–100 µCi/µg) by the method of Hunter and Greenwood (12), and the [¹²⁵I]TSH was purified by gel chromatography on Sephadex G-100. The sensitivity of the method was less than 0.5 ng/ml serum. Under the conditions of this assay 1.0 ng TSH/ml of serum is equivalent to 2 µU/ml.

Growth hormone was determined according to the method described by Catt, Niall, and Treager (13). Plasma cortisol values were determined by the method of Kliman (14), and radioimmunoassay of serum insulin was measured as described by Soeldner and Slone (15). Serum thyroxine (T₄) was measured by the method of Cassidy, Benotti, and Pino (16), and free thyroxine was determined by a modification of the method of Sterling and Brenner (17). Prolactin determinations were kindly performed by Dr. Lawrence Jacobs, Washington University School of Medicine (18). The radioimmunoassay for prolactin does not cross-react with other pituitary peptides nor with placental lactogen.

RESULTS

Postmortem examination of all the infants revealed acrania and anencephaly. Hypothalamic tissue was not identified grossly nor by microscopic brain sections in any of the infants. The brain stem was fairly well preserved in baby D, but at the mesencephalic-diencephalic junction the neural tube was flattened forming an array of cyst-like structures filled with fluid. Hypoplastic pituitary glands were identified in all subjects, and the combined adrenal glands of each infant weighed less than 1 g (normal 6–8 g). Thyroid architecture was well preserved. Baby C had an absent clitoris, but ovaries and uterus were present. Babies A and B showed large islet cells in the pancreas as previously described by Driscoll, Benirschke, and Curtis (8). Nuclear chromatin masses were present in the three phenotypic females and absent in the male.

Glucose and insulin tolerance tests. The results of the intravenous glucose tolerance tests of babies A and B are illustrated in Fig. 1. The glucose peaks observed at 10 and 15 min were higher than observed in normal neonates, and glucose disappearance was more rapid. The *Kt* values (19) (disappearance of total glucose after an

¹ Abbreviations used in this paper: GHG, human growth hormone; TRH, thyrotropin-releasing hormone; TSH, thyrotropin-stimulating hormone; T₄, thyroxine.

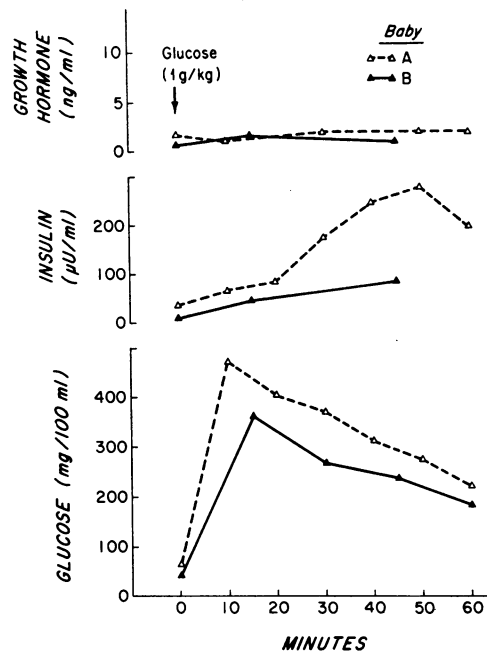


FIGURE 1 Glucose tolerance tests in anencephalic infants A and B. Intravenous glucose (1 g/kg) was administered as described in the text.

intravenous load) for glucose disappearance for infants A and B were 1.4 and 1.54%, respectively. Both infants appeared to have a delayed insulin response to the elevation of blood sugar. In baby B, however, an early insulin peak may have been missed, since the first sample was obtained 15 min after the glucose load. Serum growth hormone levels were not influenced by the test.

The lowest fasting blood sugar found in these babies was 42 mg/100 ml in baby A (at 1 h of age). Despite sustained fasting, baby C (at 4 days of age) and baby D (at 5 days of age) had blood glucose values of 70 and 80 mg/100 ml, respectively. These infants had received intravenous glucose only at the termination of insulin tolerance tests.

Babies C and D also showed a clear resistance to the hypoglycemic effects of exogenous insulin (Table I). The blood sugar of baby C fell to only 62 mg/100 ml after a dose of 0.2 U of insulin/kg. After administration of 1 U/kg to baby D, a dose 10 times higher than usually administered for insulin tolerance tests, the blood sugar decreased by only 30 mg/100 ml. The data in Table I also illustrate the failure of hypoglycemia to cause human growth hormone (HGH) release in these patients. Baby C showed an increase in cortisol from 4.1 to 15.3 µg/100 ml during the test, but serum ACTH levels did not increase. We have no explanation for this other than the possibility of a direct insulin-related effect on the adrenal.

TABLE I
Insulin Tolerance Tests

	Time	Glucose	Growth hormone	Cortisol	ACTH
	min	mg/100 ml	ng/ml	μg/ml	pg/ml
Baby C	0	90	0.2	4.1	5
	30	76	0.2	9.3	5
	45	64	0.2	—	—
	60	62	0.2	15.3	5
Baby D	0	50	1.6	—	—
	15	40	1.0	—	—
	30	30	0.8	—	—
	45	35	1.0	—	—
	60	45	0.8	—	—

Insulin tolerance tests were carried out as described in the text. Babies C and D received 0.2 and 1.0 U insulin/kg, respectively.

Thyroid status and response to thyrotropin-releasing hormone. The thyroid glands of all infants weighed between 1.8 and 2 g at autopsy; this is within the normal range for newborns. The serum thyroxine (T_4) values in all patients were between 10 and 11 $\mu\text{g}/100\text{ ml}$; the concentration of free T_4 varied between 1.8 and 2.2 $\text{ng}/100\text{ ml}$. TSH values obtained during the first 24 h of life (5–6 ng/ml) were lower than reported by others (20). The response of three of the infants to synthetic thyrotropin-releasing hormone (TRH) is shown in Table II. All infants showed active secretion of TSH with peak serum concentration values between 27 and 53 ng/ml .

Growth hormone and cortisol responses to synthetic lysine-vasopressin. The responses of growth hormone and cortisol after lysine-vasopressin administration are shown in Fig. 2. In contrast to the failure of growth hormone release after insulin administration, there was evidence of active secretion of growth hormone after injection of vasopressin. As is also shown in Fig. 2, cor-

TABLE II
Release of Thyrotropin by Exogenous Thyrotropin-Releasing Hormone

Time	Baby A	Baby B	Baby C
min			
0	5.2	5.5	4.4
10			11.0
20	27.5	53.0	21.0
30			33.0

The infants received 100 μg of thyrotropin-releasing factor intravenously. TSH values are expressed as nanograms per milliliter. 1 ng TSH is equivalent to 2 μU .

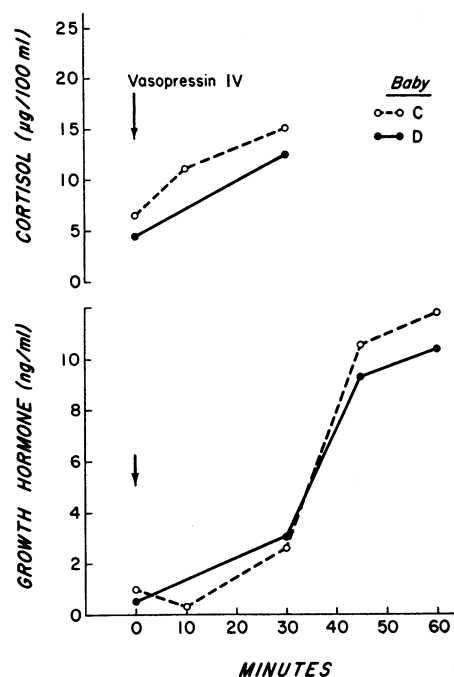


FIGURE 2 Growth hormone response of anencephalic infants to lysine-vasopressin. Vasopressin (100 μg) was administered intravenously as described in the text.

tisol levels increased to more than 100% of the basal level 30 min after vasopressin administration.

The responsiveness of the adrenals to exogenous ACTH was also determined in babies C and D. The plasma cortisol concentration increased from basal levels of less than 5 μg to 14 $\mu\text{g}/100\text{ ml}$ (infant C) and 15 $\mu\text{g}/100\text{ ml}$ (infant D) 30 min after ACTH infusion.

Prolactin measurements. Serum prolactin levels obtained on three of the infants are shown in Table III. In contrast to the low resting levels of growth hormone and TSH, the prolactin values of these infants indicated an active secretion. Samples obtained from babies B and C during the first 24 h of life were higher than the value obtained on baby D on the 4th day of life.

DISCUSSION

The role of hypothalamic-releasing factors in controlling hormone secretion from the anterior pituitary is well established (21, 22). Our studies of anencephalic infants without identifiable hypothalamic tissue have provided an opportunity to investigate pituitary and other endocrine function in infants presumably lacking endogenous releasing factors and an integrated hypothalamic-pituitary axis. The results indicate that the anterior pituitary response to provocation tests mediated via the hypothalamus is markedly altered but show that hormone secretion by the pituitary itself can be stimulated directly in the absence of hypothalamic tissue.

Basal levels of serum TSH were low (5 ng per ml) when compared with the values reported by Fisher, Odell, Hobel, and Garza (23) during the first 24 h of life but sufficient to maintain euthyroidism during intra-uterine and immediate neonatal life. The fact that TSH could be demonstrated in these patients suggests that there may be selective pituitary autonomy. The increase in serum TSH after infusion of synthetic thyrotropin-releasing hormone is similar to the response seen in patients thought to have hypothyroidism secondary to hypothalamic dysfunction (24). The large increases observed may be due to accumulation of TSH in the pituitary because of deficient endogenous stimulation and release. It would have been of interest to determine if all of the anencephalic infants lacked the surge in serum TSH normally seen immediately after birth (20, 23); however, logistical problems precluded such an evaluation.

Serum growth hormone levels have been reported to be high (30–50 ng/ml) during the first days of life (25, 26). Resting growth hormone values of the infants reported here were low or negligible, and growth hormone secretion was not stimulated by insulin-induced hypoglycemia. Although there was marked resistance to insulin, babies C and D (Table I) did sustain falls of 20–30 mg/100 ml in blood sugar without showing increases in serum growth hormone concentration. Such falls in blood sugar have been reported to be sufficient to provoke hormone secretion in normal adults (27). Cornblath, Parker, Reisner, Forbes, and Daughday (25) have shown insulin-induced hypoglycemia to be a potent stimulus to growth hormone secretion in the normal newborn. By contrast, growth hormone secretion was stimulated in these anencephalic infants after administration of lysine-vasopressin. Vasopressin appears to have a “releasing factor-like” action on anterior pituitary hormone secretion (28, 29). Kaplan and Grumbach (30) have previously reported the growth hormone concentration of anencephalic pituitaries to be in the low-normal range. The data of the present study indicate that although hypothalamic control of growth hormone secretion is absent in anencephalics, the pituitary can secrete growth hormone in response to specific stimulation. It has been reported (31) that stimulation of growth hormone secretion by insulin-induced hypoglycemia is inhibited if the hypothalamus is maintained normoglycemic. More recently, Himsworth, Carmel, and Frantz (32) provided direct evidence for specific glucose receptors in the lateral hypothalamus. The absence of such centers in anencephaly would, of course, preclude such a control system. Autoregulation of growth hormone secretion by growth hormone itself, another postulated mechanism for growth hormone control (33, 34), would also be interfered with if the sensor is in the hypothalamus.

TABLE III
Serum Prolactin Levels

	Age	Prolactin
		ng/ml
Baby B	20 h	152
Baby C	30 min	136
	4 h	148
Baby D	4 days	38

Vasopressin administration also resulted in an increase in serum cortisol levels. This has been used as indirect evidence of ACTH release (35).

In contrast with the positive control of growth hormone, TSH, ACTH, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) by hypothalamic-releasing factors, prolactin secretion appears to be controlled by a specific prolactin inhibitory factor of hypothalamic origin. Turkington, Underwood, and Van Wyk (36) have demonstrated in man that interruption of hypothalamic-pituitary relationships by surgical stalk section results in increased prolactin secretion.

Our results further support the concept that prolactin secretion is controlled by a tonic inhibitory influence of the hypothalamus. The prolactin values of the anencephalic infants in our study were well within the normal range for newborns reported by Hwang, Guyda, and Friesen (37). Although serial determinations were not performed, values obtained from babies B and C during the first 24 h of life were higher than that of baby D measured at 3 days. Hwang et al. (37) showed that the prolactin level of newborns decreased during the first days of life. Thus, the secretion of prolactin by the anencephalics probably reflects the absence of tonic inhibitory influences initiated by the hypothalamus.

Delayed parturition in anencephalic pregnancies is another disturbance that has been attributed to altered fetal hypothalamic and pituitary function. Experimentally induced destruction of the fetal lamb pituitary causes prolonged gestation in that species (38). Since the infusion of ACTH initiates parturition under those conditions, it seems likely that normal function of the fetal pituitary and adrenals contributes to the onset of labor. Because such function is ultimately controlled by hypothalamic centers, their lack in anencephaly may explain the frequent prolongation of gestation. However, definitive evidence relating the fetal adrenal to the onset of parturition in man is lacking.

The normal neonate is very sensitive to exogenous insulin (25). The stability of serum glucose levels shown by these anencephalic infants during fasting and insulin-induced hypoglycemia is of considerable interest but not well understood. Administration of 1 U/kg of

insulin (10 times the standard dose) to baby D caused only a 30 mg/100 ml fall in blood sugar. Possible mechanisms for the glucose stability and insulin resistance include an abnormal catechol or insulin response or the secretion of a diabetogenic pituitary factor. Serum catechol and fatty acid levels were not determined in the present investigation. As these studies were carried out within the first 24 h of life it is unlikely that the insulin resistance is related to starvation. It has been suggested, moreover (39), that glucose stability of anencephalic infants is related to decreased glucose utilization because of the absence of central nervous system tissue. Standard intravenous glucose tolerance tests in our subjects showed higher than normal glucose levels at 10–15 min. Also, the glucose disappearance rate (Kt) for the anencephalics was faster than reported for normals ($Kt=1.03$) (19). The results are similar to the Kt of 1.7% a minute reported for an anencephalic infant by Grunt and Reynolds (39). The increased glucose disappearance may relate to the high peak levels achieved; however, we have no satisfactory explanation for this observation. Also, urine glucose losses were not determined. Normal infants show considerable variation in insulin secretion in response to a glucose load. Bowie, Mulligan, and Schwartz (19) suggested that the slow initial rate of glucose clearance in newborns is due to delayed insulin secretion in response to a glucose load. Isles, Dickson, and Farquhar (40) reported that 8 of 10 newborns had an immediate insulin response after glucose administration. However, most of the infants in their study also had a sluggish second insulin peak at 60 min. The delayed insulin response shown by the anencephalic infants (Fig. 1) may therefore be normal and not related to the central nervous system pathology.

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