Hormonal Control of Glucose-6-phosphatase and Phosphoenolpyruvate Carboxykinase Activities in the Fetal Rat Kidney

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Summary

Triamcinolone (20 µg per fetus) administered *in utero* to term rat fetuses (day 21 of gestation) increases the activities of renal G-6-Pase and PEPCK. The absence (or marked decrease) of circulating corticosteroids in fetuses from adrenalectomized, metopirone-treated mothers has, however, no clear effect on the enzyme activities. Therefore, it is doubtful that corticosteroids play a role in the development of G-6-Pase and PEPCK activities during the fetal period of life.

In 21-day-old fetuses entirely decapitated on day 18, both enzyme activities are lower than in intact fetuses of the same litter (G-6-Pase, -48%; PEPCK, -36%). In partially decapitated fetuses, the activity of G-6-Pase remains at the control level, whereas the PEPCK activity is clearly reduced (-39%). These results strongly suggest that on the last days of gestation the hormone group of parathormone, calcitonine, or thyroxine controls the G-6-Pase activity, whereas the hypothalamo-hypophysis system is implied in the development of PEPCK activity.

Parathormone (1 unit per fetus) administered to decapitated fetuses completely restores the G-6-Pase activity. Neither rat growth hormone, synacthene, nor arginine vasopressin has significant effects on the activity of PEPCK in the kidneys of decapitated fetuses.

The administration of 0.5 µmole of dibutyryl-cAMP or cyclic adenosine 3':5'-monophosphate (cAMP) to decapitated fetuses completely restores the activity of renal PEPCK, suggesting that the development of PEPCK is controlled by cAMP-dependent hormone. The same dose of dibutyryl-cAMP has no effect on the activity of G-6-Pase; cAMP produces a slight but significant increase of this enzyme activity.

Speculation

The development of renal gluconeogenesis during the fetal period is probably controlled by several hormonal factors which do not include corticosteroids.

The hormonal control of gluconeogenesis in adult rat kidney has been extensively studied on either *in vivo* or *in vitro* systems. Isolated renal tubules (20) or isolated perfused kidney (2) has been used to study the short-term regulation of gluconeogenesis by several hormones (parathyroid hormone, catecholamines, and prostaglandins). Parathyroid hormone stimulates the gluconeogenesis from different substrates by activating the membrane-bound adenylate cyclase which increases the intracellular level of cyclic adenosine 3':5'-monophosphate (cAMP). The rise in renal cAMP augments the movement of Ca⁺⁺ (17), which may be considered as a third messenger (14). Catecholamines also stimulate the gluconeogenesis in the renal cortex via α-receptors, this effect being independent of changes in the cAMP intracellular concentration (7, 16). Recently, Morrison *et al.* (19) have demon-

strated that the kidney cortex responded to prostaglandins E₁ by increasing the cAMP production.

Long-term effects of glucocorticoids were investigated *in vivo* by Longshaw *et al.* (15). These authors observed that the administration of triamcinolone to adrenalectomized adult rat enhances the glucose-6-phosphatase (G-6-Pase) and phosphoenolpyruvate carboxykinase (PEPCK) activities. The effect of glucocorticoids on PEPCK activity has been attributed to an increase of the *de novo* protein synthesis (15, 10, 4).

The development of the renal gluconeogenesis and, more especially, of the two key enzyme activities, G-6-Pase and PEPCK, were studied in rat fetuses during the last days of gestation (3, 8, 22). Hauser and Bailey (9) investigated the effect of several hormones on the renal PEPCK activity in fetal rat; none of the tested hormones was able to produce any change of the enzyme activity. Recently, Mencher and Reshef (18) have suggested that corticosteroids could play a role in the development of the renal PEPCK activity.

In this paper, we present some arguments for a control of the development of renal G-6-Pase and PEPCK activities in kidney of rat fetuses by hormones other than corticosteroids.

MATERIALS AND METHODS

ANIMALS

Sherman female rats were mated overnight and recognized pregnant by palpation 2 wk later; in this strain, delivery occurs on the night of day 21.

CHEMICALS

Bovine parathormone (B. PTH; Eli Lilly & Co, Indianapolis, IN), synthetic salmon calcitonin (Sandoz Pharmaceuticals, Hanover, NH) were kindly supplied by Doctor J. M. Garel, rat growth hormone (National Institute of Arthritis, Metabolism, and Digestive Diseases; Rat GH B5) was supplied by Doctor A. F. Farlow, arginine vasopressin was supplied by Doctor H. Vilhardt, and metopirone was supplied by CIBA (Basel, Switzerland). Triamcinolone acetate, N₆O₂ dibutyryl cyclic adenosine 3':5'-monophosphate (dib-cAMP), and cAMP were purchased from Sigma Chemical Co (St Louis, MO), synacthene (a synthetic analogous of adrenocorticotrophic hormone) was purchased from CIBA and DL-thyroxine was purchased from ROCHE (Paris).

EXPERIMENTAL PROCEDURES

All surgical procedures were done under light ether anesthesia; at the time of sacrifice, samplings were collected under pentobarbital anesthesia.

Sources of corticosteroids available for the fetuses were suppressed following Geloso and Basset (6). Pregnant rats were adrenalectomized on day 16 of gestation and received 10 mg of

metopirone twice a day until the time of sacrifice (day 20 of gestation). Metopirone is an inhibitor of 11β steroid hydroxylase which crosses the placental barrier and, thus, inhibits the fetal adrenal gland secretions.

In other pregnant females, some fetuses were "decapitated" on day 18 of gestation following the technique described by Jost *et al.* (11, 12); total decapitation removes the fetal hypothalamo-hypophysis and the thyroid-parathyroid glands; partial decapitation only removes the fetal hypophysis and the hypothalamus. For comparison with controls, the body weight of decapitated fetuses has been corrected according to the formula: corrected body weight = measured body weight $\times$ controls body weight/body weight of controls without head. Controls are fetuses of the same litter as decapitated ones.

Hormones or nucleotides were administered into intact or previously decapitated fetuses by a single subcutaneous injection through the uterine wall after maternal laparotomy. Injection (20 μ l) were done from 5 to 24 hr before the sacrifice according to the supposed time-course of action of the tested substance. Controls were intact or decapitated fetuses of other litters given injections of the same volume of vehicle and sacrificed at the same time.

ENZYME ACTIVITIES

Fetal kidneys were quickly removed, immediately frozen in liquid N_2 , and stored at $-20^\circ C$. Cytosolic PEPCK activity (EC 4.1.1.32) was determined following the method of Ballard and Hanson (1) using a 100,000 g supernatant of kidney homogenate. Results are expressed as micromoles of $^{14}CO_2$ incorporated into malate per g of protein per min (μ moles $^{14}CO_2 \cdot g^{-1}$ Prot. min $^{-1}$). G-6-Pase activity (EC 3.1.3.9) was assayed as described by Swanson (21) using glucose-6-phosphate as substrate. Results corrected for the uncatalytic breakdown of glucose-6-phosphate and for the endogenous inorganic phosphate were expressed as μ moles of inorganic phosphate released from G-6-P per g of protein per min (μ moles inorganic phosphate $\cdot g^{-1}$ Prot. min $^{-1}$). More technical details have been given in a previous report (3).

RESULTS

EFFECTS OF CORTICOSTEROIDS

The lack (or marked decrease) of circulating corticosteroids in fetuses from adrenalectomized, metopirone-treated mothers produces an enlargement of the fetal adrenal glands which is used as a test of the effectiveness of treatment (6). As shown in Table 1, the weight of adrenal glands is increased in treated fetuses (+32%). The development of G-6-Pase and PEPCK in fetal rat kidney does not seem to depend on the adrenal glands. The slight

Table 1. Renal G-6-Pase and PEPCK activities in 20-day-old fetuses from adrenalectomized, metopirone-treated mothers

	Controls ¹	Treated fetuses ²
Adrenal gland weight (mg $\cdot 100 g^{-1}$ fetal body weight)	66 ± 5^3 (5) ⁴	87 ± 8 (11) ⁵
G-6-Pase (μ moles inorganic phosphate $\cdot g^{-1}$ Prot. min $^{-1}$)	8.2 ± 1.6 (5)	6.7 ± 0.8 (11) ⁶
PEPCK (μ moles $^{14}CO_2 \cdot g^{-1}$ Prot. min $^{-1}$)	4.6 ± 0.6 (5)	3.8 ± 0.3 (11) ⁶

¹ Controls are fetuses from intact mothers sacrificed at the same time as treated ones.

² Treated fetuses are fetuses from adrenalectomized, metopirone-treated mothers (see "Material and Methods").

³ Mean $\pm$ S.E.

⁴ Numbers in parentheses, number of experiments.

⁵ Significantly different from controls ($P < 0.01$). The increase of adrenal gland weight resulting from the lack (or a marked decrease) of circulating corticosteroids is used as a test of the effectiveness of treatment.

⁶ Not statistically significant.

Table 2. Effects of triamcinolone on renal G-6-Pase and PEPCK activities in fetal rat kidney¹

	Gestational age		
	19 days	20 days	21 days
G-6-Pase			
Control ²	6.8 ± 0.3^3 (7) ⁴	13.9 ± 1.7 (14)	14.3 ± 1.0 (4)
Triamcinolone ⁵	9.3 ± 0.7 (8) ⁶	17.6 ± 3.0 (12) ⁷	19.4 ± 1.6 (4) ⁶
PEPCK			
Control ²	5.2 ± 0.7 (5)	4.2 ± 0.4 (4)	8.6 ± 0.8 (6)
Triamcinolone ⁵	6.6 ± 0.7 (5) ⁷	7.1 ± 0.5 (6) ⁶	19.1 ± 2.1 (6) ⁶

¹ G-6-Pase activity is expressed as μ moles inorganic phosphate $\cdot g^{-1}$ Prot. min $^{-1}$, and PEPCK activity is expressed as μ moles $^{14}CO_2 \cdot g^{-1}$ Prot. min $^{-1}$.

² Controls are fetuses given injections of 20 μ l of 0.15 M NaCl (hormone vehicle) and sacrificed 18 hr later.

³ Mean $\pm$ S.E.

⁴ Numbers in parentheses, number of experiments.

⁵ Fetuses were given injections of 20 μ g of triamcinolone in 20 μ l saline solution and sacrificed 18 hr later.

⁶ Significantly different from controls ($P < 0.05$).

⁷ Not statistically significant.

difference observed between fetuses from adrenalectomized, metopirone-treated mothers and those from intact mothers is not statistically significant.

On days 19, 20, and 21 of gestation, fetuses from intact mothers were given injections of 20 μ g of triamcinolone in 0.15 M NaCl and sacrificed 18 hr later. The response of the activity of renal PEPCK to hormonal treatment seems to be age dependent (Table 2). On day 19, the difference between treated fetuses and controls given injections of 0.15 M NaCl is not significant. On day 20, there is a slight increase in the enzyme activity (+69%) which becomes more marked on day 21 (+122%). The effect of triamcinolone on the renal G-6-Pase activity is not so clear. A slight, but significant augmentation of the G-6-Pase activity is observed on days 19 and 21 (+37 and +36%, respectively); however, on day 20 of gestation the difference between treated and control fetuses is not statistically significant on account of the great variability of results.

EFFECTS OF IN UTERO DECAPITATION

Results presented in Table 3 show that in 21 day old fetuses entirely decapitated on day 18, both enzyme activities are lower than in intact fetuses of the same litter (G-6-Pase, -48%; PEPCK, -36%). In partially decapitated fetuses, the activity of G-6-Pase remains at the control level whereas the PEPCK activity is clearly reduced (-39%). The corrected body weight of operated fetuses (see "Materials and Methods") is lower than that of controls; this growth retardation, probably due to nutritional disturbances, does not affect the enzyme activities of kidney because in partially decapitated fetuses which have the lowest body weight, G-6-Pase presents the very same activity as in controls. These results strongly suggest that, on the last days of gestation, either parathormone or calcitonin or thyroxine controls the G-6-Pase activity whereas hypothalamo-hypophysis system is directly implied in the development of the PEPCK activity.

To verify these hypothesis, we attempted to restore the enzyme activities in kidney of decapitated fetuses by the administration of various hormones. For each hormone tested, three groups of fetuses have been compared: (1) fetuses entirely decapitated on day 18 of gestation given injections of hormone and sacrificed on day 21, the delay between injection and sacrifice varying from 5 to 24 hr according to the hormone used; (2) entirely decapitated fetuses from other litters given injections of the vehicle of hormone; (3) intact fetuses sacrificed at the same time as injected-

Table 3. Effects of decapitation on enzyme activities in fetal rat kidney

	Controls ¹	Total decapitation ²	Partial decapitation ²
Body weight ³ (g)	4.4 ± 0.1 ⁴ (20) ⁵	3.6 ± 0.2 (11) ⁶	3.0 ± 0.1 (18) ⁶
G-6-Pase activity (μmoles inorganic phosphate·g ⁻¹ Prot. min ⁻¹)	11.6 ± 0.7 (11)	6.0 ± 0.6 (14) ⁶	11.4 ± 0.7 (18)
PEPCK activity (μmoles ¹⁴ CO ₂ ·g ⁻¹ Prot. min ⁻¹)	10.1 ± 1.0 (10)	6.4 ± 0.5 (6) ⁶	6.2 ± 0.8 (13) ⁶

¹ Controls are fetuses of the same litter as decapitated ones.

² Decapitation was performed on day 18 of gestation according to the techniques of Jost *et al.* (11, 12); animals were sacrificed on day 21.

³ The body weight of decapitated fetuses has been corrected as following: corrected body weight = measured body weight × controls body weight/body weight of controls without head.

⁴ Mean ± S.E.

⁵ Numbers in parentheses number of experiments.

⁶ Significantly different from controls ($P < 0.05$).

Fig. 1. Effects of DL-thyroxine, B. PTH and salmon calcitonin on renal G-6-Pase activity in decapitated fetuses. Fetuses were entirely decapitated on day 18 of gestation and sacrificed on day 21. The delay between hormone injection and sacrifice varied according to the time-course of action of the tested hormone. Thyroxine (1 μg in pH 9 NaOH solution per fetus; delay, 24 hr); B. PTH (1 unit USP in 0.005 M acetic acid; delay, 16 hr); salmon calcitonin (200 ng in acetate buffer, pH 4.8; delay, 6 hr). Untreated are decapitated fetuses given injections of hormone vehicle. Results are expressed as a percentage of values observed in control (not decapitated) fetuses. Bars, ± S.E.; numbers, number of experiments. The absolute values for each control group (DL-thyroxine, B. PTH, and salmon calcitonin) are respectively: 12.2 ± 0.5 (13 experiments), 10.4 ± 0.9 (11 experiments), and 13.7 ± 0.7 (12 experiments). **, significantly different from untreated ($P < 0.01$).

decapitated ones. Results of these experiments are presented below.

EFFECTS OF THYRO-PARATHYROID HORMONES ON RENAL G-6-Pase IN DECAPITATED FETUSES (FIG. 1)

Thyroxine (1 μg per fetus; delay, 24 hr) and calcitonin (200 μg; delay, 6 hr) are unable to restore the activity of kidney G-6-Pase in decapitated fetuses to the level observed in intact ones. Differences between hormone and vehicle injections (thyroxine, NaOH pH 9; calcitonin, acetate buffer pH 4.8) are not statistically significant. Bovine parathormone administered at a dose of 1 unit per fetuses completely restores the G-6-Pase activity after a delay of 16 hr (Fig. 1), but has no effect on the activity of PEPCK (data not shown) as expected from decapitation experiments.

Fig. 2. Effects of rat growth hormone, arginine vasopressin, and synacthene on renal PEPCK activity in decapitated fetuses. Fetuses were entirely decapitated on day 18 of gestation and sacrificed on day 21. The delay between hormone injection and sacrifice varied according to the time-course of action of the tested hormone. Rat growth hormone (10 μg in 0.01 M NaOH solution per fetus; delay, 16 hr); arginine vasopressin (6 mUnits in 0.15 M NaCl solution; delay, 6 hr), synacthene (250 μg in 0.15 M NaCl solution; delay, 5 hr). Untreated are decapitated fetuses given injections of hormone vehicle. Results are expressed as a percentage of values observed in control fetuses (means ± S.E. with number of experiments). The absolute values for each control group (rat growth hormone, arginine vasopressin, and synacthene) are 10.8 ± 1.6 (11), 11.0 ± 1.3 (4), and 12.3 ± 1.2 (11), respectively.

EFFECTS OF HYPOPHYSEAL HORMONES ON PEPCK ACTIVITY (FIG. 2)

Neither rat growth hormone (10 μg per fetus; delay, 16 hr; vehicle, 0.01 M NaOH), synacthene (250 μg; delay, 5 hr; vehicle, 0.15 M NaCl), nor arginine vasopressin (6 mUnits; delay, 6 hr; vehicle, 0.15 M NaCl) have significant effects on the activity of PEPCK in the kidney of entirely decapitated fetuses.

EFFECTS OF cAMP AND dib-cAMP (FIG. 3)

Nucleotides were injected into decapitated fetuses 5 hr before the sacrifice (day 21) at a dose of 0.5 μmole per fetus. In cAMP (or dib-cAMP) injected-decapitated fetuses, the renal PEPCK activity is markedly higher than in saline injected-decapitated

Fig. 3. Effects of dib-cAMP, cAMP, and Ca^{++} on renal enzyme activities in decapitated fetuses. Fetuses were entirely decapitated on day 18 of gestation and sacrificed on day 21. Fetuses were given injections of 0.5 μmole of cAMP or dib-cAMP in 0.15 M NaCl solution (delay, 5 hr). Some of them had been given injections of cAMP (0.5 μmole) and Ca^{++} (4.5 μmoles) and sacrificed 16 hr later. Untreated are decapitated fetuses given injections of nucleotide vehicle. Results are expressed as a percentage of values observed in control fetuses (means $\pm$ S.E. with number of experiments). In G-6-Pase assays, the absolute values of control group are: 17.2 ± 0.7 (12), 13.4 ± 0.5 (28), and 14.9 ± 1.1 (5) for dib-cAMP, cAMP, and cAMP + Ca^{++} , respectively; in PEPCK assays, the control values are 10.5 ± 1.2 (8) and 9.3 ± 0.7 (17) for dib-cAMP and cAMP, respectively. *, significantly different from untreated ($P < 0.05$); **, significantly different from untreated ($P < 0.01$).

fetuses and close to the activity observed in intact fetuses. For instance, the mean value obtained after dib-cAMP administration is 9.7 ± 1.0 $\mu\text{moles } ^{14}\text{CO}_2 \cdot \text{g}^{-1} \text{Prot. min}^{-1}$ (nine experiments); values in saline-injected-decapitated fetuses and in intact fetuses are 5.0 ± 0.6 (nine experiments) and 10.5 ± 1.2 (eight experiments), respectively. There is no significant difference between intact and dib-cAMP injected fetuses.

The same dose of dib-cAMP which is able to completely restore the renal PEPCK activity has no effect on the activity of G-6-Pase. However cAMP produces a slight but significant increase of the enzyme activity. Addition of Ca^{++} (4.5 μM) to cAMP solution does not change the effect of nucleotide.

DISCUSSION

Present data show that triamcinolone administered *in utero* to term rat fetuses (day 21) increases the activities of renal gluconeogenic enzymes, this effect being more marked for PEPCK than for G-6-Pase. The effect of triamcinolone on the renal PEPCK in fetal rat has been previously demonstrated by Mencher and Reshef (18); for these authors, the hormone induces an increase in the pre-existing enzyme activity but does not cause the primary appearance of PEPCK in kidney of fetuses. Hauser and Bailey (9) administering triamcinolone into rat fetuses at a dose 25 times as high as that used in present experiments did not observe any increase of the PEPCK activity. Such a negative result is very likely due to a too short delay (5 hr) between injection and sacrifice, the time-course of the hormone effect being relatively slow (18). We have not observed any significant change in the activities of renal gluconeogenic enzymes in fetuses from adrenalectomized, metopirone-treated mothers. Blood corticosteroids concentration was not determined in these fetuses; however, the adrenal gland enlargement and the fact that the same experimental

procedure completely inhibits the development of another fetal kidney enzyme, the Na,KATPase (6), are consistent with a lack or at least a marked decrease of circulating corticosteroids. Inasmuch as the absence of hormones has no clear effect on the activities of G-6-Pase and PEPCK, it is doubtful that corticosteroids play a role in the development of these enzyme activities during the fetal period of the life. An excess of exogenous hormone either could have a trophic effect or could act on the development of gluconeogenic enzymes in synergy with specific factors.

The activities of renal G-6-Pase and PEPCK increase in rat fetuses during the last days of gestation (3). As shown in Table 3, the development of these enzymes is clearly delayed by decapitation; the activities measured on day 21 are significantly lower in fetuses previously decapitated on day 18 than in intact littermates. However, the decapitation does not entirely suppress the development of both enzymes. The activities in 21-day-old decapitated fetuses are markedly higher ($\times 3$) than those that we have recently observed in the same strain on day 18 of gestation (3). It seems very unlikely that so great a difference results from variations in animal batches, and one may conclude that part of the development of renal G-6-Pase and PEPCK activities escapes hormonal control. Normal development of the enzyme activities in fetuses probably results from an increase in the number of differentiated tubules and a maturation of tubules previously differentiated. There is no information which allows one to know whether decapitation inhibits the differentiation or the maturation (or the both) of proximal tubules. PTH stimulates gluconeogenesis in adult kidney (20) where tubular differentiation is achieved; our finding that this hormone completely restores the G-6-Pase activity in decapitated fetuses can suggest that the decapitation interferes rather with maturation than differentiation. Histologic studies could clear up this point. In decapitated fetuses, none of the tested hormones (rat growth hormone, arginine vasopressin, or synacthene) was able to restore the PEPCK activity to its normal level. It must be noticed that in these experiments, hormones were administered to fetuses submitted to a total decapitation which suppressed the thyro-parathyroid glands. As a possibility, hypophyseal hormone(s) could act in synergy with hormone(s) of the thyro-parathyroid system. Another hypothesis is that the time-course of action of the tested hormones is not respected. Finally, hormone(s) other than the tested ones could be involved. In the kidney of adult animals, hormonal treatments may produce changes in protein concentration (13); the measurements of enzyme activity based on mg protein may, therefore, not always correspond to changes in total enzyme activity per organ. In present experiments, however, the protein content in fetal kidney expressed as mg protein per g body weight does not appear to be significantly modified by the applied hormones. This may be due to the short duration of hormonal treatment; moreover, an eventual effect of hormones on the protein concentration may be masked in the fetus by the important increase of kidney protein which occurs on the last days of gestation: +460% between days 18 and 21 (6).

The administration of dib-cAMP or cAMP to decapitated fetuses completely restores the activity of renal PEPCK to the control level, suggesting that the development of PEPCK is controlled by cAMP-dependent hormone(s). It is well known that PTH stimulates the gluconeogenesis in adult kidney by increasing the renal cAMP content (20). Inasmuch as PTH completely restores a normal G-6-Pase activity in decapitated fetuses, the lack of effect of dib-cAMP and the very slight effect of cAMP on this enzyme are rather surprising. Garel *et al.* (5) have demonstrated that the removal of fetal parathyroid glands by decapitation resulted in a marked decrease in blood calcium. Because calcium ions play a key role in gluconeogenesis (14, 17), we have tested the effect of the association of cAMP with Ca^{++} on the activity of G-6-Pase in decapitated fetuses; no stimulation of the enzyme activity higher than that produced by the nucleotide alone was observed. Such a result could be explained by a difference between the time-course of action of cAMP and that of Ca^{++} , cAMP being metabolized by phosphodiesterase before Ca^{++} penetrated into the cells (?).

Further investigations are needed to clarify many points. However, present data clearly demonstrate that the development of the gluconeogenesis in the fetal rat kidney is partly controlled by hormones other than corticosteroids, one of these being the PTH which acts by enhancing the development of the G-6-Pase activity.

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