Thyroid Hormone Modulation Of Glucocorticoid-Induced Polycystic Kidney Disease


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N ormal growth and development of the mammalian kidney is partly regulated by hormones, and administration of glucocorticoid hormones (GC) at specific times during development causes polycystic kidney disease (PKD) in a number of animal species (1). In inbred mice, where metanephrogenesis continues until about the 20th postnatal day (2), the "time-window" for cyst induction by exogenous glucocorticoids extends into the first few days of life (3). Because hormonal manipulation, genetic variation, and environmental changes influence the incidence and severity of this GC-induced disease, it is consistent with a multifactorial threshold trait (1).

In the early neonatal period of both human and murine development, there are significant changes in GC and thyroid hormone (TH) metabolism (4). There are many interrelationships between the effects of TH and GC, and the receptors of these hormones act through similar and sometimes contiguous hormone-responsive elements of target genes (5). We report evidence of an effect of TH on cystogenesis in this mouse model.

METHODS

Breeding pairs of inbred C57BL/6J mice (1) were obtained from Jackson Laboratories (Bar Harbor, ME). All animal procedures were in accordance with the guidelines established by the Canadian Council on Animal Care and were approved by our institutional committee.

Seven groups of mice, including the control group, were studied. Except for the control group, they received methylprednisolone acetate (MPA) (250 mg/kg, im, at 1 day of age), triiodothyronine (T3) (1.25 mg/kg per day, ip, for 5 days) or propylthiouracil (PTU) (via maternal drinking water, 0.01% wt/vol), or a combination of these. Control mice received saline injections. On Day 5, the animals were killed, and their kidneys were removed for histological study. Cystic severity was quantified on the basis of a previously described 0 to 4+ scale (1). Thyrotropin (TSH) analysis was by competitive binding assay. The small blood volumes, taken by cardiac puncture on Day 5, necessitated pooling from 3 to 5 animals of each treatment group.

Comparison of disease incidence among groups was done using a log-linear model of the appropriate contingency table. The degrees of severity in groups receiving MPA were analyzed using the scores as dependent variables in a linear model with a model comparison approach for the 2 × 2 analysis of variance implied by the experimental design.

RESULTS

There was a significant decrease in the incidence of GC-induced cyst formation, from 86% to 64%, when T3 was given in addition to MPA (χ²(1) = 10.76, P = 0.001). There was no change in incidence with the addition of PTU to animals treated with MPA alone or MPA + T3 (χ²(2) = 0.08, P = 0.96).

The TSH levels of mice receiving PTU were more than three times as high as the levels of mice not receiving PTU, confirming biochemical hypothyroidism (TSH range: without PTU, 405 to 510; with PTU, 1877 to 5483 ng of equivalent crude pituitary extract/mL).

None of the controls showed cystic change, nor did animals receiving PTU or T3 alone. Frequencies of scores for cystic change in animals that received MPA are summarized in Figure 1. Analysis of these scores showed no significant interaction between T3 and PTU (F₁,220 = 0.075, P = 0.79) and no significant effect of PTU (F₁,220 = 2.15, P = 0.14). There was a significant reduction in the severity of cyst formation with T3 administration. The mean score decreased from 1.58 with MPA to 0.83 with MPA + T3 (F₁,220 = 15.15, P = 0.0001), which represents a reduction in cyst formation in the range of 19%.

DISCUSSION

The incidence and severity of disease is decreased by the administration of exogenous T3 in this model of GC-induced PKD. PTU-induced hypothyroidism has no effect on this phenomenon. Neither T3 nor PTU administration in the absence of GC is associated with cyst development in the kidney.

The precise mechanism of the steroid in the pathogenesis of cystic disease is not known, and neither is the mechanism of T3 action in this model. There are several possibilities. Thyroid hormone may upregulate expression of 11β-hydroxysteroid dehydrogenase en-

1 Received September 18, 1995. Accepted December 5, 1995.
2 Correspondence to J.F.S. Crocker, NWK Children's Hospital, 5850 University Avenue, Halifax, NS B3J 369, Canada.
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Thyroid and glucocorticoid hormones are important factors in normal growth, development, and maturation. It has been argued that many developmental changes that appear to be thyroid-hormone dependent, may, in fact, be corticosteroid-dependent (12), and several possible interactions between these hormones have been studied. For example, it has been noted that in rats, exogenous glucocorticosteroids depress concentrations of circulating thyrotropin (13). Newborn rats with neonatal hyperthyroidism secrete corticosterone in response to stress despite the fact that normal rats and mice have low cortisol levels and are unresponsive to stress stimulation for the first 10 days of life (14).

The induction of PKD is complex, involving many facets of growth and development, including genetic and hormonal factors and possibly alteration of the rate of metanephrogenesis. This study addresses the issue of effects of altered thyroid-hormone status on in vivo cystogenesis and shows that thyroid hormone reduces GC induction of cysts in the neonatal mouse.

REFERENCES