A Possible Role for Pituitary Function in the Age-Dependent Regulation of Hepatic Tyrosine Aminotransferase Activity

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Received March 31, 1971

SUMMARY

A single injection of adrenocorticotropic hormone (ACTH), as well as that of glucagon, into rat fetuses evokes the premature appearance of hepatic tyrosine aminotransferase (TAT), an enzyme whose initial appearance normally occurs shortly after birth. TAT activity is detectable in fetal liver after 2.5 hours, peaks at approximately 4 hours and is maintained at adult levels for at least another 2 hours. In contrast, the induction of this enzyme by the above-mentioned stimuli in liver of sexually mature rats is spontaneous and transient. Alterations in temporal expression of enzyme induction may be a general reflection of hormonal fluctuations which accompany development and aging.

The primary function of hormones in biochemical differentiation may be that of regulators in the expression of genetic information, as discussed previously (1). Undoubtedly, certain mechanisms of hormonal interaction, in turn, are susceptible to control by various aspects of pituitary function. The purpose of the present report is to demonstrate the ability of ACTH to regulate hormonal interaction, as expressed by either the premature appearance of TAT activity in fetal rat liver or its induction from basal levels in the liver of sexually mature rats.

EXPERIMENTAL PROCEDURE

Animals - Young, normal male rats of the Sprague-Dawley strain, pur-

chased from Charles River Breeding Farms, were maintained on a commercial stock diet and used at 2-months of age. Pregnant, female rats also purchased from Charles River, were timed to arrive during the sixteenth day of gestation.

Chemicals and Materials - All biochemical reagents were purchased from Boehringer - Mannheim, Calbiochem or Sigma. Glucagon was obtained from Calbiochem, cortisol acetate from Nutritional Biochemicals, Iletin insulin from Eli Lilly Laboratories and ACTH from National Drug.

Enzyme Assay - TAT activity was prepared from fetal or adult liver and assayed as described previously (2).

RESULTS AND DISCUSSION

As illustrated in Figure 1, following a single injection of ACTH or glucagon the activity of hepatic TAT increases markedly in 21-day rat fetuses, as well as in intact, 2-month old rats (3). However, both degree and time course of these enzyme adaptations vary with increasing age. In fetal liver, enzyme activity is evoked prematurely from undetectable levels to 1.7 units per g of liver. Appearance of enzyme activity is first observed at 2.5 hours and peaks at 4 hours following administration of either hormone. This prematurely evoked level of activity is maintained for at least 2 hours. A similar observation following administration of glucagon was reported by Greengard and Dewey (4), although the degree of response was much smaller and data were presented at only a single time point. No effect of insulin or cortisol on TAT activity is detectable in fetal liver.

In contrast, in liver from young adults enzyme activity is increased from a basal level of 1.3 to a maximum of 8.4 units per g of liver following administration of ACTH. This increase in enzyme activity is characterized by a 2-fold change in as little as 30 minutes and a maximal increase at approximately 2.5 hours after hormonal injection. This essentially spontaneous response is very transient, its decay beginning almost immediately thereafter. A similar time course and degree of TAT adaptation are initia-

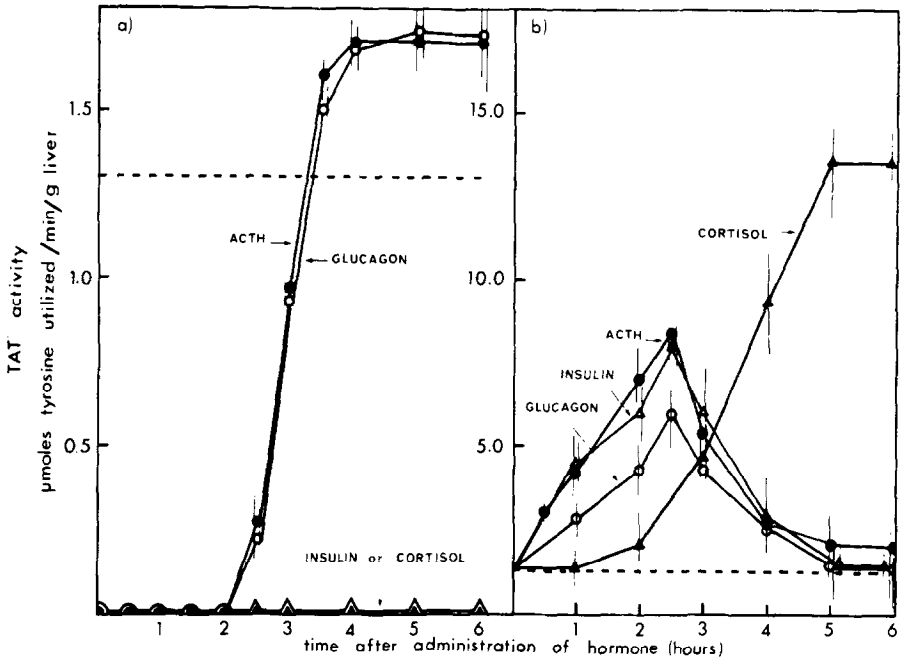

Figure 1. Age-Dependent Hormonal Control of TAT Activity

All hormones were administered by a single intraperitoneal injection in the following amounts per kg of body weight: ACTH, 25 units; glucagon, 2 mg; insulin, 10 units; and cortisol, 60 mg. Fetal injections were administered in utero, based on an estimate of body weight obtained by weighing fetuses of the same age although from pregnant females not utilized for enzyme studies. Curves representing each of the hormonal administrations to a) 21-day fetuses or b) 60-day old males are indicated on the Figures. No attempt was made to distinguish sex of the fetuses. The broken horizontal line in each case represents basal levels of TAT activity, characteristic of the 60-day old male. Although data are not indicated, administration of identical volumes of the appropriate solvent for each hormone, distilled water for insulin, glucagon or cortisol and 0.5% phenol in water for ACTH, produced undetectable changes in TAT activity at either age. Each value represents the mean and range of 3 to 5 fetuses or adults.

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ted following administration of glucagon or insulin, but not cortisol, to 2-month old rats.

There are at least 3 alternative mechanisms by which ACTH may elicit an increase in hepatic TAT activity. 1) The commercially obtained ACTH preparation may be contaminated by another substance(s) which is capable of increasing TAT activity. However, the enzyme adaptation is not detectable in 2-month old adrenalectomized rats (5), a condition in which at least cortisol

(6), insulin (7) or glucagon (7) is effective. 2) ACTH may interact directly with the liver, increasing TAT activity in a manner similar to insulin, glucagon or cortisol, each of which is effective also in isolated, perfused liver (8). For the identical reasons presented in rebuttal to the previous mechanism, this possibility is unlikely also. Furthermore, preliminary experiments fail, thus far, to demonstrate the effect of ACTH in isolated, perfused liver (9). 3) ACTH may interact with one or more endocrine tissues, eliciting release of a substance(s) which, in turn, stimulates directly the hepatic enzyme adaptation. Since ACTH elicits secretion of at least corticosteroids and insulin (10, 11), this general mechanism probably encompasses the most likely explanation.

Physiological dogma favors utilization of a pituitary-adrenal route. However, the time course of the cortisol-mediated adaptation is such that this increase in TAT activity begins by the time response either to stress (12) or to ACTH (Figure 1) is decaying. That the physiological response to either certain conditions of stress or administration of ACTH, as expressed by fluctuations in hepatic TAT activity, probably results from a complex interaction involving adrenal and pancreatic hormones, is the subject of a separate report (5).

Physiological delays in the time required to initiate certain enzyme adaptations, including the response by TAT to administration of ACTH, recently were proposed to be a general biochemical manifestation of senescence (3,5, 13-15). It is evident from the data presented above that susceptibility of adaptive enzymes to the temporal regulation of their activity varies also during early development. The extent to which endocrine gland response to pituitary control or the availability of pituitary hormones influences the temporal expression of enzyme fluctuation remains to be determined both during early development and senescence.

ACKNOWLEDGEMENTS

The author gratefully acknowledges Mrs. Kathleen Bare for her excellent technical assistance. This work was aided by Grants HD-04382-01 from the National Institute of Child Health and Human Development, and P-592 and P-202K from the American Cancer Society.

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