Effects of Estrogen, Glucocorticoid, Glucagon, and Adenosine 3′:5′-Monophosphate on Catalytic Activity, Amount, and Rate of de Novo Synthesis of Hepatic Histidase*

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The mechanisms by which estrogen, glucocorticoid, glucagon, and adenosine 3′:5′-monophosphate (cAMP), regulators which participate in the postnatal development of rat liver histidase, elevate the catalytic activity of this enzyme have been explored. A monospecific antibody against homogeneously purified preparations of rat liver histidase has been elaborated in the goat. Employing this antibody in immunotitration experiments, it has been demonstrated that the elevations of hepatic histidase activity elicited by administration in vivo of estradiol-17β, cortisol acetate, glucagon, and N,N'-dibutyryl adenosine 3′:5′-monophosphate (dibutyryl cAMP) are paralleled, in each instance, by equivalent increments in immunoprecipitable histidase protein. Following administration of each of the three hormones and dibutyryl cAMP, rates of 14C-leucine incorporation in vivo into rat liver histidase, isolated by immunoprecipitation, relative to incorporation rates into total soluble hepatic protein, increase in magnitudes which are comparable to increases in enzyme amount and catalytic activity. It is thus inferred that estrogen, glucocorticoids, and glucagon, via cAMP, each regulate rat liver histidase development at specific postnatal stages by inducing increases in histidase biosynthetic rates.

Hepatic l-histidine ammonia-lyase (histidase, EC 4.3.1.3) of the rat undergoes a complex postnatal developmental course, in which its catalytic activity initially appears shortly following parturition and subsequently rises in a multiphasic sex-specific fashion, resulting in enzyme levels which are considerably higher in the adult female than the male (1, 2). Reports from this and other laboratories suggest that this developmental course is the resultant of concerted action of a number of hormones and nutritional factors acting at strategic stages, some of which elevate enzyme activity (e.g. estrogen, glucocorticoid, glucagon via cAMP (3–7), and amino acids (4, 5, 8, 9)) and others of which suppress histidase activity (e.g. pituitary components (10, 11), androgen (12), and thyroxine (13, 14)). Since the postnatal development of liver histidase is dependent on such a complex interplay of regulators, it provides a valuable model for investigation of biochemical mechanisms underlying hormonal regulation of enzymes in differentiating tissues.

In the present study, we have explored the mechanisms by which estrogen, glucocorticoid, and glucagon, as well as cAMP (the presumed mediator of glucagon action) effectuate increases in hepatic histidase catalytic activity. It has been previously shown that each of the three hormones is capable of elevating histidase activity only at specific developmental stages characteristic for each hormone (6, 7); glucagon is capable of increasing enzyme activity at all postnatal stages; estrogen, only subsequent to the first neonatal month, and glucocorticoid, only during the first 2 postnatal months but not in mature animals. We have thus chosen rats at 1 month of age, a stage at which all three hormones and cAMP are capable of histidase activity enhancement, for this study on underlying mechanisms of hormonal regulation of this enzyme. For each regulator we have inquired as to whether elevation in histidase activity is due to quantitative increments in amounts of the identical enzyme protein and, if so, whether such increments are a result of specific increases in rates of de novo histidase synthesis. To quantitate histidase protein by methods other than catalytic activity and to measure enzyme synthetic rates, we have employed, respectively, immunotitration and radioactively labeled amino acid incorporation into specifically immunoprecipitated enzyme, employing a monospecific antibody elaborated against homogeneous rat liver histidase.

Preliminary reports on these studies have been presented (15, 16).

MATERIALS AND METHODS

Purification of Histidase—Livers of 18 female (250 to 300 g) Sprague-Dawley rats (Marland Breeding Farms, Hewitt, N.J.) were used for the isolation of histidase (Table I). Animals were killed by decapitation and to each 8-g portion of liver, 24 ml of 10 mM Tris, pH 7.2, containing 14 mM MgCl₂ and 0.6 M KCl, was added (17). The contents were homogenized in a Potter-Elvehjem homogenizer, centrifuged at 122,000 × g for 30 min with occasional stirring, followed by cooling. The thermally denatured protein was removed by centrifugation for 30 min at 66,000 × g. Following addition of 20 ml of glycero/100 ml of supernatant, the fraction precipitating between 35 and 50% ammonium sulfate saturation was collected. This precipitate was suspended in a minimum amount of 20 mM potassium phosphate buffer, pH 7.2, containing 20% glycerol, 0.1 mM MnCl₂, and 1 mM glutathione (Buffer A), dialyzed against two changes of this buffer, and applied to a DEAE-cellulose column (2.5 × 90 cm)
equilibrated with Buffer A. The column was washed with Buffer A until one large protein peak was eluted, as measured by absorbance at 280 nm. A 1600-ml linear gradient of 0 to 1.6 M NaCl in Buffer A was then applied. Eluate fractions were assayed for histidase; the most active fractions were pooled and concentrated to 5 ml in an Amicon ultrafiltration cell fitted with a PM-30 membrane. This material was applied to a Sephadex G-200 column (2.5 x 90 cm), equilibrated with Buffer A. The column was washed with Buffer A until the eluate was free of protein and a 250-ml linear gradient of 0.02 to 0.12 M potassium phosphate, pH 7.2, containing 0.02% gelatin, 0.1 M NaCl, and 1 mM glutathione, was then applied. Fractions demonstrating constant high specific activity (approximately 5.0) were pooled, designated as the purified enzyme, and employed as antigen to elicit anti-histidase antibodies in goats. The purification procedure employed, although similar initial conditions, was reported for rat liver histidase by Kalkur et al. (19) and Brand and Harper (20), differs in its later steps and results in a 250-ml linear gradient of 0.02 to 0.12 M potassium phosphate, pH 7.2, containing 0.02% gelatin, 0.1 M NaCl, and 1 mM glutathione, as the column most active fractions were pooled, designated as the purified enzyme (approximately 5.0) were pooled, designated as the purified histidase was observed by Klee (21).

**Histidase Assay** - The enzyme assay mixture consisted of 85 mM pyrophosphate buffer, pH 9.2, 4 mM glutathione, and 41 mM L-histidine; enzyme was added to initiate the reaction. Optimal activity was monitored at 277 nm in a recording Gilford spectrophotometer, model 2000, thermostated at 37°. Enzyme activities were calculated from the linear portions of the curves, in the region of zero order kinetics, using an extinction coefficient of 18,500 for the reaction product, urocanate (22). One unit of enzyme activity is defined as the amount producing 1 μmol of urocanic acid/min under the conditions described. The sensitivity of this assay was 0.005 unit of activity. Specific activity is defined as enzyme units per mg soluble protein, as measured by the method of Lowry et al. (23).

**Acrylamide Gel Electrophoresis** - Analytical acrylamide gel electrophoresis carried out according to the procedure of Davis (24) in 7.5% gels at pH 8.3 at 4°. A current of 3 mA/gel was applied for 3 h. The sensitivities of purified Pseudomonas histidase was observed by 30.

**Preparation of a Monospecific Antibody Prepared against Rat Liver Histidase** - Antiserum to rat liver histidase was obtained in the following manner. Purified homogenous histidase (250 to 300 μg) was emulsified in an equal volume of complete Freund's adjuvant. This preparation demonstrated histidase-neutralizing ability and was tested for monospecificity in Ouchterlony immunodiffusion and immunoprecipitation systems with the same antisera (26).

**Hormone and Cyclic AMP Injection Schedule** - Twenty-eight-day-old birth-dated Sprague-Dawley rats were administered eight daily subcutaneous injections of the following agents, per 100 g of body weight: 1 mg of glucagon (Eli Lilly and Co.), 5 mg of N0'-dibutyryl-adenosine 3'-5'-monophosphate monosodium dihydrate (Calbiochem, Andrew) plus 3 mg of theophylline (Nutritional Biochemicals Corp.), 5 μg of estradiol-17β (Chemed, Inc.), 3 mg of cortisol acetate (Calbiochem). Controls received appropriate volumes of either propylene glycol (estradiol-17β solvent) or 0.9% NaCl (diluent for other injected materials).

**Rates of Histidase Biosynthesis Relative to Total Soluble Protein** - Radioisotope incorporation studies were carried out on rats which were injected intraperitoneally with 20 μCi of uniformly labeled [1-14C]leucine (New England Nuclear Corp.) per 100 g of body weight. They were killed 1 h after having received injection of hormone or dibutyryl cAMP. Following a 45 min incorporation period, the animals were killed by decapitation and 25% liver homogenates in 10 mM Tris, pH 7.2, containing 14 mM MgCl2 and 0.6 M KCl were prepared.

**Rates of isotopic incorporation into immunoprecipitated histidase** were determined as follows. A portion of liver homogenate was incubated at 55° for 20 min, cooled, and centrifuged at 66,000 × g for 20 min. The supernatants were used for determination of incorporation of radioactive into total protein. One-half milliliter of these high speed supernatants was precipitated with 3 ml of 10% trichloroacetic acid; the precipitates were washed three times with 3 ml of 10% trichloroacetic acid and dissolved in 0.5 M NaOH for radioactive counting in Bray's solution (27) and for protein assays (23).

**Inmunotitrations** - Constant amounts of antibody were incubated with increasing levels of antigen (heat-treated nonradioactive liver cytosol, prepared as above). Immunoprecipitation was carried out as described above. Following centrifugation of the immunoprecipitates, the supernatants were assayed for residual histidase activity and any washed precipitates were assayed for protein (23). Control precipitations were made for protein precipitated by nonimmune serum. A portion of immunoprecipitated liver histidase activity was neutralized with homogenate, as determined by prior immunotitration, allowed to remain at room temperature for 30 min, and incubated overnight at 4°. The immunoprecipitates were collected by centrifugation, washed twice in 0.15 M NaCl, and solubilized in 0.5 M NaOH for radioactive counting in a Tri-Carb Spectrometer, model 3310 for protein determination (23). Quantitative immunoprecipitation of homogeneity was assumed. The measurement of immunoprecipitated radioactivity was followed by solubilization of proteins in 0.5 M NaOH for radioactive counting in Bray's solution (27) and for protein assays (23).

**Rates of histidase biosynthesis** were determined as described above. A portion of liver homogenate was incubated at 55° for 20 min, cooled, and centrifuged at 66,000 × g for 20 min. The supernatants were used for determination of incorporation of radioactive into total protein. One-half milliliter of these high speed supernatants was precipitated with 3 ml of 10% trichloroacetic acid; the precipitates were washed three times with 3 ml of 10% trichloroacetic acid and dissolved in 0.5 M NaOH for radioactive counting in Bray's solution (27) and for protein assays (23).

**Table I**

| Purification of histidase from female rat liver | Purification step | Volume (ml) | Total activity (μg) | Total protein (mg) | Specific activity (μg/μg) | Yield (μg/μg) |
|---------------------------------------------|-----------------|------------|-------------------|------------------|---------------------|-------------|
| 1. Homogenate                               | 504 236         | 39 254     | 0.006 100         |                  |                     |             |
| 2. High speed supernatant (122,000 x g)    | 405 205         | 12 958     | 0.016 87          |                  |                     |             |
| 3. 55°, 30 min                              | 356 187         | 8 926      | 0.027 79          |                  |                     |             |
| 4. 35 to 50% saturated (NH4)2SO4            | 30 165          | 1 138     | 0.118 70          |                  |                     |             |
| 5. DEAE-cellulose                           | 184 124         | 276       | 0.450 53          |                  |                     |             |
| 6. Sephadex G-200                          | 137 103         | 86        | 1.19 44           |                  |                     |             |
| 7. Hydroxyapatite                           | 40 72           | 14        | 5.10 30           |                  |                     |             |

1. The abbreviation used is: dibutyryl cAMP, N0'-dibutyryl-adenosine 3':5'-monophosphate.
RESULTS

Characteristics of Purified Rat Liver Histidase and Its Antibody - Disc electrophoresis of freshly prepared native enzyme (Table I, Step 7) on nondenaturing acrylamide gels revealed a single protein band upon aniline blue black staining (Fig. 1). Measurement of histidase activity on such gels, by the eosin-staining technique, demonstrated one enzyme activity band which corresponded to the protein-stained band. Liver histidase, as purified by the above described procedures, thus migrates as a single homogeneous enzymatic species, free of protein contaminants. That this enzyme preparation has been purified to homogeneity has been further affirmed by the findings of constant high specific activities in the most active fractions of the final purification step, hydroxylapatite chromatography, and upon rechromatography on DEAE-cellulose; a single subunit band following sodium dodecyl sulfate-polyacrylamide electrophoresis; and sedimentation as a single species following analytical ultracentrifugation.

Immunoglobulin preparations of goat antisera withdrawn following immunization with purified histidase preparations were tested for monospecificity in the Ouchterlony double diffusion system. Antibody preparations were obtained which yielded a single precipitin band, when diffusing against a high speed supernatant of female rat liver homogenate; this band fused with a reaction of identity with that of purified histidase (Fig. 2). These antibody preparations were thus monospecific. Moreover, unfractionated cytosols and purified histidase prepared from male rat liver also yielded single precipitin bands, which formed lines of identity with each other and with the female enzyme. Thus, although hepatic histidase activity in the adult female liver is more than double that in male (3), histidases present in the livers of both sexes are immunologically identical.

Effects of Estrogen, Glucocorticoid, Glucagon, and Cyclic AMP on Amounts of Histidase Protein - Table II depicts a typical experiment in which administration in vivo of eight daily doses of glucagon, dibutyryl CAMP plus theophylline, estradiol-17β, or cortisol acetate, in triplicate animals, elevated hepatic histidase activity in 28-day-old male rats to 167, 122, 200, and 152%, respectively, of control values. In an attempt to determine whether these hormonal elevations in enzyme activities are due to corresponding increases in amounts of enzyme protein, increasing amounts of heat-treated liver cytosols from these animals were immunotitrated with constant amounts of anti-histidase, as described under "Materials and Methods." Fig. 3 illustrates that identical equivalence points were observed with liver preparations from untreated control animals and those receiving estradiol-17β, cortisol acetate, glucagon, or dibutyryl CAMP plus theophylline, in whom histidase activity levels were elevated. In each case, a given quantity of antibody precipitated identical amounts of catalytic activity, following which further added histidase was recoverable in the supernatant. Furthermore, measurement of the protein content of the immunoprecipitates indicated that, in each case, as the antigen/antibody ratio increased progressively, increasing amounts of protein were precipitated, followed by a plateau at the equivalence zone, then a decrease in precipitable protein in the region of antigen excess. The point of maximum protein precipitation was in good agreement with that of the equivalence point, as determined by supernatant enzyme assays; approximately equal amounts of protein were precipitated per unit of catalytic activity under each experimental condition. It may be inferred from these two immunochemical measurements of histidase, that all elevations in histidase catalytic activity following treatment with estradiol-17β, cortisol acetate, glucagon, and CAMP are a result of proportionate increases in the quantity of immunologically identical histidase protein.

Effects of Estrogen, Glucocorticoid, Glucagon, and Cyclic AMP on Rates of de Novo Histidase Synthesis - To determine
Effects of glucagon, cAMP, estrogen, and glucocorticoid on hepatic histidase activity

| Treatment            | Histidase activity | % control |
|----------------------|---------------------|-----------|
| Control              | 0.44 ± 0.04        | 100       |
| Glucagon             | 0.74 ± 0.07        | 167       |
| Dibutyryl cAMP       | 0.54 ± 0.04        | 122       |
| Estradiol-17β        | 0.88 ± 0.05        | 200       |
| Cortisol acetate     | 0.67 ± 0.06        | 152       |

**Fig. 3.** Immunotitration of hepatic histidase from the untreated rats (△) and rats treated with glucagon (○), cAMP (●), estradiol-17β (■), and cortisol acetate (■), depicted in Table II. Constant amounts (0.125 ml) of anti-histidase immunoglobulin preparation were incubated with increasing amounts of heat-treated liver cytosols, containing the histidase activities indicated on the abscissa, and assayed for residual enzyme activity recoverable in the supernatants and precipitable protein, as described under "Materials and Methods." Each symbol represents the mean of results from triplicate animals.

Whether the observed increases in catalytic activity and amount of enzyme protein following estradiol-17β, cortisol, glucagon, and CAMP administration are due to increased histidase biosynthetic rates, the amounts of L-[14C]leucine incorporation into the total soluble protein, were compared in control and treated animals. Table III demonstrates that a doubling enzyme activity upon glucagon administration was accompanied by a comparable rise in L-[14C]leucine incorporation into histidase, relative to that into the total soluble protein, were compared in control and treated animals. Table III demonstrates that a doubling enzyme activity upon glucagon administration was accompanied by a comparable rise in L-[14C]leucine incorporation into histidase, relative to that into the total soluble protein. Similarly, the 40% rise in enzyme activity following dibutyryl cAMP (plus theophylline) administration was paralleled by a 61% increase in relative synthetic rate of histidase. Furthermore, rats receiving estradiol-17β, whose enzyme activities are 76% of control values manifested a doubling in the rate of relative histidase synthesis. An increase of 76% in catalytic activity following cortisol acetate administration was accompanied by a 52% higher rate of relative histidase synthesis. Thus, all hormonally induced elevations in histidase catalytic activity and in amounts of enzyme protein are accompanied by approximately parallel increases in in vivo biosynthetic rate of the enzyme.

To evaluate the identity and purity of the immunoprecipitates, 14C-labeled immunoprecipitates were analyzed by sodium dodecyl sulfate-acrylamide gel electrophoresis. Fig. 4 depicts densitometric tracings and radioactive measurements of a typical stained sodium dodecyl sulfate electrophoretic gel.
which rates of incorporation of $[^{14}C]$leucine into immunoprecipitated histidase, relative to that incorporated into total soluble protein, indicate that these hormonal elevations in histidase catalytic activity and quantity are accompanied by similar increases in rates of in vivo biosynthesis of the enzyme. Approximately 0.03% of the total soluble hepatic protein synthesized in control weanling rats was histidase, whereas between 0.05% and 0.06% of the total soluble hepatic protein was synthesized in animals treated with each of the hormones and dibutyryl cAMP (Table III). These data are compatible with earlier findings of hormonal induction of histidase by the protein synthesis inhibitors, cycloheximide and ethionine (3, 6, 7). Since approximately equivalent increases in synthetic rate, amount of enzyme protein, and catalytic activity occur in each case, it is reasonable to assume a causal relationship among these three parameters, i.e. each of these regulators induces an increase in enzyme synthetic rate, which results in an increased amount of enzyme protein and thus enhanced catalytic activity. Enhancement of enzyme synthesis seems to wholly account for the observed elevations in histidase levels and activity. Thus there seems to be no need to invoke other mechanisms for these hormonal influences on histidase, e.g. decreased degradation rate (30), enzyme protein conformational change, or the production or destruction of activators or inhibitors, respectively. Indeed, no evidence of alterations in levels of dissociable activators or inhibitors could be demonstrated in the estrogenic enhancement of histidase (3).

Cyclic AMP has been shown to activate numerous protein kinases, which, in turn, phosphorylate and thereby alter the catalytic efficiency of certain enzymes (e.g. phosphorylase, glycogen synthetase, 31). In these instances, post-translational alteration in enzyme activity, not synthetic rate change, is the mechanism of cAMP action. However, cAMP-mediated enhanced enzyme synthesis has been demonstrated in Escherichia coli (32) and eukaryotes (33-35), among which rat liver histidase may be included. The possible intermediate role of protein kinase action in the phosphorylation of various nuclear or ribosomal proteins, as suggested by Wicks (36) may indeed be applicable to the cAMP induction of hepatic histidase.

The validity of the conclusion that the hormonally enhanced $[^{14}C]$leucine incorporation into immunoprecipitated histidase is a true reflection of increased enzyme synthetic rates is based on several assumptions: (a) that both histidase and other soluble proteins are synthesized from the same leucine pool; possible alterations in the specific activity of this leucine pool among individual animals or as a result of hormonal or cAMP treatment are nullified by expression of incorporation rates into histidase relative to those into total soluble protein; and (b) that histidase was completely and specifically immunoprecipitated. Complete precipitation was assured by addition of 50% antibody excess and by confirmation that neither enzyme nor marker proteins (15, 37).

Normal postnatal developmental increases in this hepatic enzyme in both sexes have been previously demonstrated to be accompanied by corresponding increments in amounts and biosynthetic rates of histidase (37-39). Each of the three hormones, shown in this study to induce elevated rates of histidase biosynthesis, have been previously demonstrated to participate in the development of this enzymic activity at specific postnatal developmental stages: glucagon (via cAMP) and glucocorticoid, in the neonatal emergence (7); glucocorticoid, in the male (7), and estrogen, in the female (3), adolescent developmental increases of this enzyme. Thus, it may be concluded from both previous and present studies that the mechanism of postnatal development of hepatic histidase is enhancement of de novo enzyme biosynthesis by various hormones at specific developmental stages.

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