Enzyme Induction and Modulation

edited by V. A. Najjar

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V.A. NAJJAR
Division of Protein Chemistry
Tufts University School of Medicine
Boston, Massachusetts, U.S.A.

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Preface

In addition to performing its prime function as a vehicle for scientific communications of varied colorations, *Molecular and Cellular Biochemistry* is again focusing on two subjects which it treats in depth. One of these is a book issue dealing with the transglutaminase reaction. The other is this issue that deals with induction and modulation of enzymes. This is a very broad subject that calls for broader coverage than could be included in one book issue. However, I have elected to include only certain contributions that serve as general examples of the principles involved.

There are six articles on enzyme regulation in hepatocyte culture. These include arginase and argino-succinate synthetase, γ-glutamyl transferase and plasminogen activitor. Other regulatory enzymes that are discussed are protein kinases, 2,3-bisphosphoglycerate synthetases, carbamoyl phosphate synthetase, heme oxygenase, cytochrome P-450, tyrosine hydroxylase, fatty acid synthetase, acetyl CoA carboxylase, among others. Also included is the regulation of several enzyme messengers RNAs.

As in the past, subscribers to the journal will receive this double volume as a continuation of regular issues of the journal *Molecular and Cellular Biochemistry*. This double volume will also be available separately in the form of a book issue to interested readers through Martinus Nijhoff Publishers.

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Part I

Molecular and Cellular Biochemistry 53/54, 11-21 (1983).

Hormonal regulation of plasminogen activator in rat hepatoma cells

Thomas D. Gelehrter, Patricia A. Barouski-Miller, Patrick L. Coleman and Bernard J. Cwikel
Departments of Internal Medicine and Human Genetics, University of Michigan Medical School, Ann Arbor, MI 48109, U.S.A.

Summary

Plasminogen activators are membrane-associated, arginine-specific serine proteases which convert the inactive plasma zymogen plasminogen to plasmin, an active, broad-spectrum serine protease. Plasmin, the major fibrinolytic enzyme in blood, also participates in a number of physiologic functions involving protein processing and tissue remodelling, and may play an important role in tumor invasion and metastasis. In HTC rat hepatoma cells in tissue culture, glucocorticoids rapidly decrease plasminogen activator (PA) activity. We have shown that this decrease is mediated by induction of a soluble inhibitor of PA activity rather than modulation of the amount of PA. The hormonally-induced inhibitor is a cellular product which specifically inhibits PA but not plasmin. We have isolated variant lines of HTC cells which are selectively resistant to the glucocorticoid inhibition of PA but retain other glucocorticoid responses. These variants lack the hormonally-induced inhibitor; PA from these variants is fully sensitive to inhibition by inhibitor from steroid-treated wild-type cells. Cyclic nucleotides dramatically stimulate PA activity in HTC cells in a time- and concentration-dependent manner. Paradoxically, glucocorticoids further enhance this stimulation. Thus glucocorticoids exert two separate and opposite effects on PA activity. The availability of glucocorticoid-resistant variant cell lines, together with the unique regulatory interactions of steroids and cyclic nucleotides, make HTC cells a useful experimental system in which to study the multihormonal regulation of plasminogen activator.

Introduction

Plasminogen activators (PAs) are membrane-associated arginine-specific serine proteases found in a variety of tissues (1). PA selectively hydrolyses a single Arg-Val bond of the plasma zymogen, plasminogen, to yield the active serine protease, plasmin, the major fibrinolytic activity in blood (2, Fig. 1). Plasmin is a broad-spectrum endopeptidase which can act on a variety of proteins. Because plasminogen is present in plasma in relatively high concentrations (1.5 to 2 μM, or 0.5% of all plasma proteins), the plasminogen activator-plasmin cascade provides considerable potential proteolytic activity (2, 3). Thus generation of plasmin both amplifies PA activity and broadens the substrate specificity. In addition to plasmin's well-known role in fibrinolysis, it is also involved in many normal physiologic functions which involve protein processing, cell migration and tissue remodelling (1, 3, 4, Table 1). By acting directly on fibrin and directly or indirectly (via activation of procollagenase) on connective tissue matrix (5, 6), the plasminogen activator-plasmin cascade may also play an important role in tumor invasion and metastasis (1, 3, 4, 6).

Not surprisingly for an enzyme of such biological importance, plasminogen activator is subject to regulation by a variety of effectors (see 7 for review). Steroid (8-16) and polypeptide hormones